Leishmaniasis

The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted in an AAALACi accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.
Leishmaniasis

• Diverse group of diseases caused by infection from protozoan parasites of the genus *Leishmania*

• Designated one of the five most important diseases worldwide by the WHO
  – 1.5 to 2 million new cases/year

• Leishmaniasis threatens over 350 million individuals in 88 countries, and directly impacts US service members abroad
Over 2000 cases of Leishmaniasis have occurred in American troops deployed to Iraq and Afghanistan since 2001.
An scourge of many names…

- Aleppo evil
- Baghdad boil
- Biskra nodule
- Jericho button
- Lahore sore
- pian bois (bush yaws)
- chiclero’s ulcer
- uta
- sandfly disease
- espundia
- black fever
- Dum-Dum fever
- kala-azar

Sir William Boog Leishman (1865-1926)
Vector
-Female Sand fly
- *Lutzomyia* in the Americas
- *Phlebotomus* elsewhere
- Poor flyers, remain near ground
- World wide distribution
- Bites at exposed areas and clothing lines

Reservoirs
- Humans
- Dogs
- Rodents
Transmission* and Lifecycle

Promastigotes divide and migrate to the anterior midgut and foregut.

Sand fly injects promastigotes into the skin during a blood meal. *infective stage

Promastigotes are phagocytized by neutrophils that are rapidly recruited to the bite site.

Infected neutrophils release the parasites, which are then consumed by macrophages.

Amastigotes transform into promastigotes in midgut.

Ingestion of parasitized cell.

Sand fly ingests infected macrophages when it takes a blood meal.

Amastigotes multiply in cells (including macrophages) of various tissues. *diagnostic stage

Promastigotes transform into amastigotes inside macrophages. *diagnostic stage
Disease

• Three clinical syndromes:
  – **Cutaneous (skin)**
    • Localized, diffuse, *Leishmania recidivans*, post kala-azar dermal leish.
  – **Mucocutaneous** (mouth, nose, also called “espundia”)
  – **Visceral** (internal organs, also called “kala-azar”)

• Each syndrome can be caused by multiple different *Leishmania* species, and many species can cause multiple different syndromes
  – Determined by species of parasite, location of infected macrophages, and individual immune response.
Highly Endemic Areas

• 90% of cutaneous leishmaniasis occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria.

• 90% mucocutaneous leishmaniasis occur in Bolivia, Brazil, and Peru.

• 90% of all visceral leishmaniasis cases occur in Bangladesh, Brazil, India, Nepal, and Sudan.

WHO Leishmaniasis: Burden of Disease
Cutaneous Leishmaniasis (CL)

• Overwhelming majority of Leishmaniasis
  – 1 to 1.5 million cases/year
• Endemic in widely scattered regions throughout the world
• Generally not life-threatening, but potentially permanently disfiguring
• Wide spectrum of clinical presentations that differs somewhat between New and Old World due to regional *Leishmania* species
Old World Cutaneous Leishmaniasis

Fig. 277-2A. Distribution of cutaneous leishmaniasis (CL). A, Old World (Eastern Hemisphere) CL. B, New World (Western Hemisphere) CL. Other species causing CL in the New World are not shown but can be found in Table 277-1.
New World Cutaneous Leishmaniasis

Fig. 277-2B. Distribution of cutaneous leishmaniasis (CL). A, Old World (Eastern Hemisphere) CL. B, New World (Western Hemisphere) CL. Other species causing CL in the New World are not shown but can be found in Table 277-1.

Copyright © 2015 by Saunders, an imprint of Elsevier Inc.

PPID, 8th ed., pg. 3093
Common CL Presentations

- New World CL
  - Localized disease
  - Diffuse disease
  - Disseminated disease
  - Mucosal disease*

- Old World CL
  - Localized disease
  - Diffuse disease
  - Post-kala-azar dermal leishmaniasis
  - Leishmaniasis recidivans

*Mucocutaneous Leishmaniasis (espundia) is considered distinct from CL

PPID, 8th ed., pg. 3099
"In some cities infection is so common and so inevitable that normal children are expected to have the disease soon after they begin playing outdoors, and visitors seldom escape a sore as a souvenir. Since one attack gives immunity, Oriental sores appearing on an adult person in Baghdad brands him as a new arrivat .."

- Chandler A., in "Introduction to Parasitology" 1944

Chiclero’s Ulcer

• Localized cutaneous leishmaniasis (ear)
• Majority of cases caused by *L. mexicana*
• Chicleros – men who collect the chicle latex from which chiclets chewing gum is made

*Can Med Assoc J* 1986; 134: 216

Photo: Dr. Jason Blaylock
Diffuse Cutaneous Leishmaniasis

• Multiple diffuse spreading nodules
  – Do not ulcerate
  – Generally face and extremities

• Protracted course - May be lifelong!

Jericho Buttons

www.loc.gov
Disseminated Cutaneous Leishmaniasis

• Characterized by hundreds of lesions
  – Papules, nodules, ulcers, acne-like
• Seen in Brazilian agricultural workers and immunocompromised
• Low parasite burden
• May involve mucosa

www.ajtmh.org
Post-kala-azar Dermal Leishmaniasis (PKDL)

- Follows treatment of visceral leishmaniasis
  - up to 4 years later
- Macules progressing to papules, nodules and verrucous (wart-like) forms
  - May resolve or remain chronic (up to 20 years)
  - Can be confused with leprosy

Fig. 277-7. Post-kala-azar dermal leishmaniasis. Papular lesions after the treatment of visceral leishmaniasis in Kenya.

PPID, 8th ed., pg. 3097
PKDL

USUHS teaching slides
Leishmaniasis recidivans

• Small papules that spread outward leaving a central scar
  – frequently on face

• Chronic
  – waxes and wanes
  – difficult to treat
  – may recur

Leishmaniasis Recidivans Recurrence after 43 Years: A Clinical and Immunologic Report after Successful Treatment

Mary A. Marovich,1,6 Rosalia Lira,1 Marc Shepard,2 Glenn H. Fuchs,3 Richard Kruetzer,4 Thomas B. Nutman,1 and Franklin A. Neva1

1Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and Departments of 2Medicine and 3Dermatology, George Washington University, and 4Walter Reed Army Institute of Research, Washington, DC
Mucucutaneous Leishmaniasis (ML)

- 2-5% of persons with New World CL develop mucous membrane involvement
  - Nose, oral cavity, pharynx, larynx
  - Concurrent or months to decades after CL resolves (can also be primary presentation)
  - Can be severely mutilating and life-threatening

www.who.int
Long-standing cases

PPID, 8th ed., pg. 3099
Visceral Leishmaniasis (VL)

- Leishmanial infection of the internal organs
- Unlike CL, generally similar in all regions
- Incubation: 2-8 months (10 days to >1 year)
- Wide spectrum of presentations
  - majority asymptomatic (6.5-18:1 ratio)
  - asymptomatic to subacute to severe multi-organ disease
  - can spontaneously resolve over weeks to months, or progress to fatality if not treated
Visceral Leishmaniasis in the Old World

90% of visceral leishmaniasis in 5 countries: Bangladesh, India, Nepal, Sudan and Brazil.

Geographic distribution of main species of Old World visceral leishmaniasis:
- Sporadic cases
- Endemic area of *L. infantum*
- Endemic area of *L. donovani*
- Hyperendemic area of *L. donovani*

Fig. 277-3A. Distribution of visceral leishmaniasis (VL). A, Old World (Eastern Hemisphere) VL. B, New World (Western Hemisphere) VL.

Copyright © 2015 by Saunders, an imprint of Elsevier Inc.
Visceral Leishmaniasis in the New World

Fig. 277-3B. Distribution of visceral leishmaniasis (VL). A, Old World (Eastern Hemisphere) VL. B, New World (Western Hemisphere) VL.

Copyright © 2015 by Saunders, an imprint of Elsevier Inc.

PPID, 8th ed., pg. 3094
kala-azar (black or fatal sickness)

• Severe VL
  – Classic pentad: prolonged fever, weight loss, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia
• Progressive (variable rates)
• > 90% mortality within first two years
• Can be opportunistic infection in immunocompromised state
Viscerotrophic Leishmaniasis from Desert Storm (L. tropica)

• Rare, low-grade, syndrome first identified in 8 patients returning from Operation Desert Storm
  – Fevers: 6 of 8
  – Weight loss: 2 of 8
  – Nausea, vomiting, low-grade watery diarrhea: 2 of 8
  – Lymphadenopathy: 2 of 8
  – Hepatosplenomegaly: 2 of 8
  – Anemia: 3 of 8
  – Leukopenia or thrombocytopenia: 0 of 8
  – Elevated liver enzymes: 6 of 8
  – No symptoms: 1 of 8

• Similar syndromes since found in Brazil and Italy

Magill et al, NEJM 1993:328(19)
Diagnosis

• Clinical Diagnosis

• Cutaneous Leishmaniasis
  – Biopsy/Aspiration/Scraping
  – Amastigotes in a smear
  – Promastigotes in culture
  – PCR of sample (DNA/RNA)

• Visceral Leishmaniasis
  – Biopsy of Bone Marrow or Spleen
    • Touch Prep, PCR, Culture
  – Immunologic
    • rK39 leish. antigen direct agglutination test
These images depict a wound or lesion that is being treated with injections. The text accompanying these images indicates that the treatment should aim to catch edge of the most affected tissue and avoid including adjacent to the lesion. At least one half of biopsy
Tissue Diagnosis – skin, spleen, bone marrow

- Infected Macrophage with amastigotes
  - a nucleus (red arrow)
  - a rod-shaped kinetoplast (black arrow).
Diagnosis - culture

Promastigotes

Photo: CDC

Photo: www.msu.edu
Diagnosis

Montenegro Skin Test

- AKA Leishmanin Test
- Injection of dead promastigotes into skin
  - DTH Reaction (wheal) suggests infection
- Not licensed in U.S

PCR

Real-Time PCR

During each extension cycle, the Taq DNA polymerase cleaves the reporter dye from the probe

L. major
L. major
L. V. panamensis

Negative control

Cycle

ΔRn
• Leishmania Diagnostics Laboratory


• usarmy.detrick.medcom-wrair.mbx.leishmania-diagnostic@mail.mil

• Juan Mendez - **240-595-7353**

• ID or Dermatology Electronic Consult Service
Treatment

• Treatment is not standardized
  – What works on one species and clinical presentation may fail in another
  – Must adapt to regional experience
  – Much is anecdotal and off-label

• In general, treatments result in clinical cure, but not parasitical cure
  – Lifelong potential for reactivation in immunocompromised
Treatment Options

**CL**
- Watchful waiting
- Local destructive therapies
  - Liquid NO₂
  - Thermo-Med device
- Topical creams
  - Paromomycin
- Systemic treatment
  - Amphotericins (Ambisome)
  - Pentavalent Antimonials
    - Sodium stibogluconate (Pentostam)*
    - Meglumine Antimoniate (Glucantime)
- (Glucantime)
  - Azoles (Fluconazole, Ketoconazole, Itraconazole)
  - Pentamidine
  - Miltefosine (Impavidol)**

**ML, VL**
- Systemic treatment
  - Pentavalent Antimonials
    - Sodium stibogluconate (Pentostam)*
    - Meglumine Antimoniate (Glucantime)
  - Azoles (Fluconazole, Ketoconazole, Itraconazole)
  - Amphotericins (Ambisome)***
  - Miltefosine (Impavido)**
  - Paromomycin
- Alone or in combination

Available in US on IND
** Only Drug FDA approved for CL in US
***Only drug FDA approved for VL in US
## CL-When to consider doing nothing

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>FAVORS NO TREATMENT</th>
<th>TREATMENT USUALLY INDICATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and direction of healing</td>
<td>Clearly improving compared to prior month</td>
<td>Worsening lesions</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>One or a few</td>
<td>&gt;5 and in different locations</td>
</tr>
<tr>
<td>Complexity</td>
<td>Uncomplicated</td>
<td>Restricts movement or wearing of clothes, cosmetic concerns</td>
</tr>
<tr>
<td>Size of lesion(s)</td>
<td>Small (&lt;1 cm)</td>
<td>Very large (&gt;5cm)</td>
</tr>
<tr>
<td>Immune status</td>
<td>Immunocompetent</td>
<td>Immunocompromised</td>
</tr>
<tr>
<td>Mucosal involvement</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Location</td>
<td>Nonexposed skin</td>
<td>Exposed skin, especially facial</td>
</tr>
<tr>
<td>L. braziliensis?</td>
<td>No or unlikely</td>
<td>Yes or likely*</td>
</tr>
<tr>
<td>How bothersome to patient</td>
<td>No or little concern</td>
<td>Very concerned or preoccupied</td>
</tr>
<tr>
<td>and family?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If Bolivia, Brazil, Peru, should be treated with systemic therapy due to risk of mucosal involvement

Adapted from PPID, 8th ed., pg. 3104
Watchful Waiting

• CL due to *L. major* (MON-26) in Saudi Arabia
  – Healing time (after study enrollment)
    • 6 weeks – 6%
    • 3 months – 34%
      – Alrajhi, *et al.*, NEJM 2002; 346

• CL in Guatemala
  – *L. mexicana* healing/cure – 68% (avg. 14 wks)
  – *L. braziliensis* healing/cure – 6% (avg. 13 wks)
    • Herwaldt, *et al.*, J Infect Dis 1992; 165
No Treatment

- CL acquired in Afghanistan
- Evaluated in Nov 2008 with 3 cm ulcer
- No treatment
- Follow-up in Jun 2009

Photo courtesy of Dr. Julie Ake
Locally Destructive Therapies

LNO₂

- Freezes lesions to kill parasites
- May cause hypopigmentation
- Not standardized
  - Cyroprobe suggested
- Painful / blister formation

ThermoMed

- Heats lesions to kill parasites
- ~ 70% efficacy in CL caused by *L. major* in Iraq and *L. tropica* in Afghanistan

Reithinger, et al CID 2005

Photo: Dr. Glenn Wortmann
Topical Cream: Paromomycin

• Aminoglycoside

• Compounded
  – 15% paromomycin
  – +/- 0.5% gentamicin

• Apply to affected area twice a day x 28 days

• 81% cure - *L. major*

Systemic Treatment: Miltefosine

- Phosphocholine analogue
- Oral
- 28 day regimen
  - 50mg po bid x 28 days
- Used worldwide for all forms of Leishmaniasis
- FDA approved for CL only (2014)

- Side effects:
  - nausea, vomiting, abdominal pain
  - LFT abnormalities
  - Increased creatinine

- Teratogenic – Do not Use in Pregnancy!
Systemic Treatment: Azoles

- Fluconazole
- Ketoconazole, Itraconazole
- Limited data
- Variable regimens
  - Oral
  - 4-6 weeks or longer
  - Weight based
- Variable efficacy
Fluconazolo le

- Prospective study
  - 200mg daily for 42 days
    - 6 weeks: 29% vs 6% placebo
    - 3 months: 79% vs 34% placebo

Alrajhi. et al. NEJM 2002;346:891
Interventions for Old World cutaneous leishmaniasis (Review)

Authors conclusions

Most trials have been designed and reported poorly, resulting in a lack of evidence for potentially beneficial treatments. There is a desperate need for large well conducted studies that evaluate long-term effects of current therapies. We suggest the creation of an international platform to improve quality and standardization of future trials in order to inform clinical practice.

In Leishmania major infections, there was good RCT evidence of benefit of cure around 3 months after treatment when compared to placebo for 200 mg oral fluconazole (1 RCT n = 200, RR 2.78; 95% CI 1.86, 4.16), topical 15% paromomycin + 12% methylbenzethonium chloride (PR-MBCL) (1 RCT n = 60, RR 3.09; 95% CI 1.14, 8.37) and photodynamic therapy (1 RCT n = 60, RR 7.02; 95% CI 3.80, 17.55). Topical PR-MBCL was less efficacious than photodynamic therapy (1 RCT n = 65, RR 0.44; 95% CI 0.29, 0.66). Oral pentoxifylline was a good adjuvant therapy to intramuscular meglumine antimoniate (IMMA) when compared to IMMA plus placebo (1 RCT n = 64, RR 1.63; 95% CI 1.11, 2.39)

In Leishmania tropica infections, there was good evidence of benefit for the use of 200 mg oral itraconazole for 6 weeks compared with placebo (1 RCT n = 20, RR 7.00; 95% CI 1.04, 46.95), for intraleisional sodium stibogluconate (1 RCT n = 292, RR 2.62; 95% CI 1.78, 3.86), and for thermotherapy compared with intramuscular sodium stibogluconate (1 RCT n = 283, RR 2.99; 95% CI 2.04, 4.37).

Systemic Treatment: Antimonials

- Sodium stribogluconate (Pentostam)
  - Investigational New Drug
  - Available from the CDC for civilians
  - Available from Walter Reed for military
  - Regimen
    - CL: intravenous 20mg/kg/day for 10-20 days
      - Outside US is often given intra-lesionally
    - VL: intravenous 20mg/kg/day for 28 days
Pentostam®

• Toxicities
  – Elevated amylase/lipase ~95%
  – Elevated liver enzymes ~50%
  – Arthralgias/myalgias ~65%
  – Rare significant EKG changes/cytopenias
  – Dermatological ~10%
    • Wide range of presentations
    • Herpes zoster virus (shingles)

DO NOT USE IN PREGNANCY

Systemic Treatment: Amphotericins

- Liposomal Amphotericin B (Ambisome)
  - Drug of choice for VL
  - Regimen (IV)
    - Immunocompetent
      - 3 mg/kg/day on days 1-5, 14, and 21
    - Immunocompromised
      - 4 mg/kg/day on days 1-5, 10, 17, 24, 31, 38
  - No established regimen for CL
  - Extensive side-effect profile
L. guyanensis - Fr Guiana
Ambisome for 7 doses
Systemic Treatment: Pentamididine

• No longer recommended for VL due to high toxicity
• One indication only
  – Short course (2 IM injections of 4mg/kg) has been found to be effective for CL caused by *L. guyanananensis* in French Guyana and Surinam only
Systemic Dosing Summary

• **CUTANEOUS LEISHMANIASIS**
  - Pentostam – 20 mg/kg IV x 10 -20 days
  - Ambisome (liposomal amphotericin B)
    - 3 MG/KG ON DAYS 1-5, 14, & 21
  - Fluconazole – 8 mg/kg/day (4 – 12 weeks)
  - Miltefosine –50mg po twice a day x 28 days

• **VISCERAL LEISHMANIASIS**
  - Ambisome (liposomal amphotericin B) 3 mg/kg on days 1-5, 14, & 21
  - Pentostam – 20 mg/kg IV x 28 days
  - MILTEFOSINE –50MG PO TWICE A DAY X 28 DAYS
Systemic Dosing Summary

• **CUTANEOUS LEISHMANIASIS**
  - Pentostam – 20 mg/kg IV x 10-20 days
  - Ambisome (liposomal amphotericin B)
    • **3 MG/KG ON DAYS 1-5, 14, & 21**
  - Fluconazole – 8 mg/kg/day (4 – 12 weeks)
  - Miltefosine –50mg po twice a day x 28 days

• **VISCERAL LEISHMANIASIS**
  - Ambisome (liposomal amphotericin B) 3 mg/kg on days 1-5, 14, & 21
  - Pentostam – 20 mg/kg IV x 28 days
  - **MILTEFOSINE –50MG PO TWICE A DAY X 28 DAYS**
Prevention

• Sandflies bite and are active at night (warmer months)
• Stay **indoors** between dusk and dawn
• Keep dogs and susceptible animals indoors at night
• Use fans - sandflies are **poor fliers** deterred by wind
• Sandflies are **small and can get through mesh** netting if not extremely fine
• House **construction** and modification; sandflies breed in cracks of houses
• Insecticides on people and animals
• Help from entomologists
• Dog vaccine available in Brazil

http://www.cfsph.iastate.edu/Factsheets/pdfs/leishmaniasis.pdf
Summary – Leishmaniasis

• Worldwide distribution
• Many species with different disease presentations
• Cutaneous form may be self-limited
• Think about mucocutaneous disease, especially in South America
• Resources available for diagnosis (WRAIR)
• Treatment response varies with species and host
Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old World, Cutaneous Disease:</td>
<td>L. tropica; L. major; L. aethiopica</td>
</tr>
<tr>
<td></td>
<td>L. tropica can cause visceral disease</td>
</tr>
<tr>
<td>Old World, Visceral Disease:</td>
<td>L. donovani complex with 3 species (L. donovani, L. infantum, and L. chagasi)</td>
</tr>
<tr>
<td>New World, Cutaneous disease:</td>
<td>L. mexicana complex with 3 main species (L. mexicana, L. amazonensis, and L. venezuelensis)</td>
</tr>
<tr>
<td>New World, Cutaneous and Mucocutaneous disease</td>
<td>Subgenus Viannia with 4 main species (L. (V.) braziliensis, L. (V.) guyanensis, L. (V.) panamensis, and L. (V.) peruviana)</td>
</tr>
<tr>
<td>New World, Visceral Disease</td>
<td>L. chagasi</td>
</tr>
</tbody>
</table>
Leishmaniasis is endemic in Texas

Figure 2. Predicted current distributions for leishmaniasis vector species.

http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0000585
What Other South American tropical disease is transmitted by sandflies?

• Bartonellosis (Carrión's disease)
  – Also called Oroya Fever or Peruvian warts
  – Peru, Andes mountains
  – Bartonella bacilliformis

• Traveler infection is not common
• Fever, myalgia, headache, and anemia
• High mortality – 40%
• Chronic infection
• Rifampin, chloramphenicol
  TMP/SMX, Streptomycin