Disclaimers

Including:

The views expressed do not necessarily represent those of the Centers for Disease Control and Prevention
principles & perspective
Leishmaniasis

Leishmaniasis is a parasitic disease with multiple forms, most notably, visceral (VL), cutaneous (CL), & mucosal (ML)

Leishmania parasites are:

- **Unicellular** (protozoan parasites)
- **Intracellular** (obligate intracellular pathogens)
- Spread by phlebotomine sand flies
PATHOGENS: "tiny" (~2-5 μm), intracellular PARASITES

VECTORS: "tiny" (~2-3 mm), inaudible SANDFLIES
Leishmaniasis: Multiple . . .

- Syndromes (forms)
- *Leishmania* species (>20 infect humans)
- Sandfly species (~30 are vectors)
- Ecologies & transmission cycles (~88 countries)
  - Tropics & subtropics to southern Europe
  - Jungles to deserts
  - Rural to urban
  - Zoonotic to anthroponotic
- Host factors (*eg*, immunogenetics)
Specificity amidst diversity
(and vice versa)
Simplicity amidst complexity
(and vice versa)
Don’t generalize or oversimplify

The multitudinous combinations of:

- **heterogeneous** *Leishmania* species/strains, syndromes, & geographic areas
  - further modified by host factors & immunoinflammatory “responses”

- may be associated with **diverse** manifestations of infection & **diverse** responses to particular therapies
Leishmaniasis
(Leishmania spp.)

**Sandfly Stages**

1. Sandfly takes a blood meal (injects promastigote stage into the skin)

2. Promastigotes are phagocytized by macrophages

8. Divide in midgut and migrate to proboscis

7. Amastigotes transform into promastigote stage

6. Ingestion of parasitized cell

5. Sandfly takes a blood meal (ingests macrophages infected with amastigotes)

**Human Stages**

2. Promastigotes transform into amastigotes inside macrophages

4. Amastigotes multiply in cells (including macrophages) of various tissues

3. I = Infective Stage

4. d = Diagnostic Stage

http://www.dpd.cdc.gov/dpdx
Leishmaniasis
(Leishmaniasis)
Leishmaniasis
(~2M cases/yr)

Visceral leish
(~0.5 million cases/yr)

Cutaneous leish (CL)
(~1.5 million cases/yr)

Old World CL
(~75% of CL cases)

New World CL
(~25% of CL cases)
Where is leishmaniasis found?

- Overall, **VL** is found in focal areas of ~65 countries:
  - But most (>90%) of the world’s cases occur in the Indian subcontinent (India, Bangladesh, and Nepal), Sudan, & Brazil

- Overall, **CL** is found in focal areas of ~88 countries:
  - But most (>90%) of the world’s cases occur in 8 countries: Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, and Syria *Old World*; & Brazil and Peru *New World*
Caveat

Cases evaluated in the U.S. reflect travel & immigration patterns & foreign affairs / policies
Visceral leishmaniasis

- **Species:** typically, *L. donovani & L. infantum (chagasi)*
- **Spectrum:** asymptomatic to life threatening
- **Incubation period:** typically, weeks to months (can be years in persons who become immunocompromised)
- **Onset:** abrupt or gradual
- **Stereotypical manifestations:** fever, weight loss, hepatosplenomegaly (especially, splenomegaly), & pancytopenia (low blood counts)
- **Severe (advanced) cases** typically are fatal, if untreated
Visceral leishmaniasis
— classic “kala-azar” —
— caused by *Leishmania donovani* —

WHO/TDR/Crump; Image 9706884
Dermotropic
Cutaneous leishmaniasis
How is the diagnosis parasitologically confirmed?

&

How often is the diagnosis parasitologically confirmed?
Leish: Diagnostic approaches

• Clinical & epidemiologic

• Parasitologic
  - Amastigotes (on a “slide”)
  - Promastigotes (in culture)
  - Parasite DNA

• Immunologic
  - Serology (helpful primarily for classic VL)
  - Delayed type hypersensitivity (skin test not licensed in the U.S.)
  - Other (investigational)
A-mastigote

Axoneme
Basal body
Kinetoplast
Nucleus

PRO-mastigote

Flagellum
Basal body
Kinetoplast
Nucleus
Tissue form = amastigote (note nucleus & kinetoplast in each amastigote)
In association with

Operations Desert Storm/Shield,

DoD identified:

- ~20 cases of CL ("dermotropic leish"); *L. major*
- ~12 cases of "viscerotrophic leish"; *L. tropica*
"Viscerotropic leishmaniasis" from Desert Storm:
the first 8 (of 12) cases documented by DoD

Table 1. Clinical Presentation of Eight Male Patients with Visceral Leishmaniasis, at the Time of Confirmatory Culture.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Incubation Period (Mo)</th>
<th>Signs and Symptoms at Presentation</th>
<th>Fever</th>
<th>Abdominal Pain*</th>
<th>Malaise*</th>
<th>Fatigue*</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>Adenopathy</td>
<td>Yes</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>Hepatomegaly, splenomegaly, adenopathy</td>
</tr>
<tr>
<td>2</td>
<td>1–4</td>
<td>Fever</td>
<td>Yes</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>Normal findings</td>
</tr>
<tr>
<td>3</td>
<td>2–8</td>
<td>Gastroenteritis</td>
<td>No</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>4</td>
<td>2–6</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Normal findings</td>
</tr>
<tr>
<td>5</td>
<td>4–12</td>
<td>Chronic fatigue with hepatosplenomegaly</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>+ + +</td>
<td>Hepatomegaly, splenomegaly</td>
</tr>
<tr>
<td>6</td>
<td>7–14</td>
<td>Chronic fatigue with adenopathy</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>+ + +</td>
<td>Hepatomegaly, adenopathy</td>
</tr>
<tr>
<td>7</td>
<td>1–6</td>
<td>Mononucleosis</td>
<td>Yes</td>
<td>+ /−</td>
<td>+ + +</td>
<td>+</td>
<td>Normal findings</td>
</tr>
<tr>
<td>8</td>
<td>3–12</td>
<td>Fever of unknown origin</td>
<td>Yes</td>
<td>+</td>
<td>+ +</td>
<td>+</td>
<td>Hepatomegaly, splenomegaly</td>
</tr>
</tbody>
</table>

*One plus sign indicates that the patient reported the symptom when questioned by the examiner; two plus signs, that the patient himself reported the symptom without questioning; and three plus signs, that the symptom was the primary one. Patient 7, represented by the plus–minus sign, reported abdominal pain of brief duration associated with diarrhea.

#7: also had illness a/w HIV seroconversion
#8: also had newly diagnosed renal cancer

(Magill et al., NEJM 1993)
Operations Desert Storm / Shield

VS

Operations Iraqi & Enduring Freedom
Leish: Risk assessment

• Place
  - Area of X country
  - Microfoci of sand fly “activity”
  - “Force of infection” in a particular place & time

• Personal factors & activities
  - Type, timing (day vs night), duration (but 1 infected bite is “enough”); sleeping conditions; use of protective measures; . . .
Patient who has leishmaniasis

What are the Rx goals?
(Individualize care of each patient)

Ideally, want 100% effective & safe, 1-dose, oral Rx targeted to amastigotes (in phagolysosomes of macrophages), which it KILLS, causing complete & lasting sterile cure & immunity
Individualized care

• Is Rx indicated? What is the worst that could happen with no or suboptimal Rx (eg, death, substantial morbidity, mucosal leish)?

• Should a drug regimen that usually is highly & rapidly effective be used, or could a potentially less effective & less toxic but more easily administrable Rx be tried 1st?
Individualized care

• Does the patient have other medical disorders that could affect the course of the leish infection or increase risk for toxic effects of certain drugs?

• Which therapeutic agents are available?

  ➢ What is known about their efficacy & toxicity profiles for treating the species of interest from the region of interest?
CL: motivations to treat

- Patient’s goal: **Heal lesions** faster than they would spontaneously ... & ... w/o a scar
- **Prevent** relapse of local lesions
- **Prevent / Rx** local dissemination (eg, lymphadenopathy, sporotrichoid spread)
- **Prevent / Rx** mucosal leishmaniasis
- **Prevent** transmission of infection, if humans could be reservoir hosts
Leish: Parenteral therapies

- Pentavalent antimonials *(CDC IND)*
- Conventional ampho B *(off label)*
- Lipid formulations of ampho B *(AmBisome: FDA approved for Rx of VL)*
- Pentamidine *(off label)*
- Paromomycin *(not available in US)*
- Immunotherapies *(investigational)*
CL: to Rx or not to Rx .... When is a modestly effective Rx good enough?
Exposure → Leish

- Asymptomatic infection
  - Rx’d
  - Self healed
  - Still infected?
- Years of asx infection
  - Leish
    - Rx’d
    - Self healed
    - Immunosuppression, trauma, ….