CHALLENGES IN CUTANEOUS LEISHMANIASIS

Perspectives of treatment development and disease control

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Leishmaniasis is endemic in 98 countries/territories with more than 350 million people at risk.

Leishmaniasis ranks as the leading NTD in terms of mortality and morbidity with an estimated 50,000 deaths in 2010 (Lozano et al., 2012) and 3.3 million disability adjusted life years (Murray et al., 2012).

0.7 to 1.3 million new CL cases occur annually worldwide.

Every 40 seconds there is a new case of CL.

Eastern Mediterranean region contribute to ~60% of global CL burden.

CL is one of the top 10 skin diseases among tourists returning from endemic countries with skin problems.

Clinical and epidemiological diversity:

CL is a most neglected disease = Neglected populations.
Global reported and estimated incidence of CL

<table>
<thead>
<tr>
<th>Region</th>
<th>Reported CL cases/year</th>
<th>Countries with 5 years of data</th>
<th>Estimated annual CL incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas</td>
<td>66,941</td>
<td>14/20 (70%)</td>
<td>187,200 to 307,800</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>155</td>
<td>5/15 (33%)</td>
<td>770 to 1500</td>
</tr>
<tr>
<td>East Africa</td>
<td>50</td>
<td>0/6 (0%)</td>
<td>35,300 to 90,500</td>
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<tr>
<td>Mediterranean</td>
<td>85,555</td>
<td>17/26 (65%)</td>
<td>239,500 to 393,600</td>
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<tr>
<td>Middle East to Central Asia</td>
<td>61,013</td>
<td>16/18 (89%)</td>
<td>226,200 to 416,400</td>
</tr>
<tr>
<td>South Asia</td>
<td>322</td>
<td>2/2 (100%)</td>
<td>1900 to 3500</td>
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<tr>
<td>Global total</td>
<td>214,036</td>
<td>53/87 (61%)</td>
<td>690,900 to 1,213,300</td>
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</tbody>
</table>

### WHO Targets and milestones for Leishmaniasis control and elimination

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone 1</th>
<th>Milestone 2</th>
<th>Milestone 3</th>
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<tbody>
<tr>
<td>2014</td>
<td>Aim to detect and treat &gt;90% of cases of visceral Leishmaniasis and post-kala-azar dermal Leishmaniasis in the South-East Asia Region</td>
<td>Complete district-level epidemiological assessment and mapping of cutaneous and visceral Leishmaniasises in 50% of endemic African countries</td>
<td>Update treatment policy for co-infection with visceral Leishmaniasis and HIV using best available evidence</td>
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<tr>
<td>2015</td>
<td>Aim to detect and treat all cases of visceral Leishmaniasis and post-kala-azar dermal Leishmaniasis in the South-East Asia Region</td>
<td><strong>Detect and manage &gt;70% of cases of cutaneous Leishmaniasis in the Eastern Mediterranean Region</strong></td>
<td>Detect and treat &gt;90% of cases of cutaneous, mucocutaneous and visceral Leishmaniasises in the Region of the Americas</td>
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<tr>
<td></td>
<td>Complete district-level mapping of cutaneous and visceral Leishmaniasises in all endemic African countries</td>
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<tr>
<td>2016</td>
<td>Detect and treat 90% of visceral Leishmaniasis cases in all endemic African countries</td>
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<tr>
<td>2017</td>
<td>Aim to verify &lt;1 case/10,000 population per year in 80% of endemic districts and subdistricts in the South-East Asia Region</td>
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<tr>
<td>2020</td>
<td>Reduce the incidence of visceral Leishmaniasis to &lt;1 case/10,000 population per year at district and subdistrict levels in the South-East Asia Region</td>
<td><strong>Aim to detect and treat all cases in the African Region, Region of the Americas, the European Region and the Eastern Mediterranean Region</strong></td>
<td>Detect and manage 85% of cutaneous Leishmaniasis cases in all endemic countries</td>
</tr>
</tbody>
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Adapted from D. Argaw
Challenges in Disease Control

- No effective vaccine is available.
- Traditional vector control methods do not appear to be effective and are often not available to or practical for at-risk populations.
- No rational measures for the control of reservoir hosts are available in the New World.
- Control is unlikely to be achieved by a single intervention. A combination of case management strategies, integrated vector control and animal reservoir control if relevant, is required and should be tailored to each context.
- The priority for control is developing and implementing improved diagnostic methods and better treatments that are more amenable to field use.
Why do we need to treat CL?

- Accelerate healing
- Minimize scarring
- Prevent complicated forms (RCL, DCL, MCL)
- Reduced transmission in ACL

One size does not fit all
Spectrum of CL lesions and Tx. Options

Adapted from M. Grogl

No Tx | Local topical | Systemic oral | Systemic parenteral | Combinations

- Multiple applications
- Painful
- Difficult to administrate
- Cosmetic problems
- 1-4 small lesions

- Variable efficacy
- Teratogenic
- GI and renal problems
- Availability
- Cost

- Toxicity
- Painful
- Difficult to administrate
- Low patient compliance
- Efficacy is decreasing

The “gap”

Topical & oral drug, safe, effective against all forms of CL, with superior cosmetic results, at a low-cost and easy to use in rural areas.

Drugs for Neglected Diseases initiative
Considerations for the treatment of CL

1. **Clinical characteristics of the lesion(s)**
   - Number of lesions
   - Type of lesion (ulcers, nodules, plaques)
   - Lesion’s size
   - Anatomical localization
   - Over infections

2. **Parasite characteristics**
   - Different species and natural history of the infecting *Leishmania* parasite
   - Parasite intrinsic variability

3. **Host Factors**
   - Age & Gender
   - Concomitant diseases
   - Host immune status
   - Patient’s behaviours and perceptions

4. **Other Factors**
   - Drug availability
   - Cost
   - Travellers, displaced and refugees populations
### 2010 WHO Recommendations

#### Recommended treatment regimens for NW CL

**No anti-leishmanial treatment**

**Local therapy, all species**
- 15% paromomycin and 12% MBCl twice daily for 20 days (B)
- Thermotherapy: 1–3 sessions with localized heat (50 °C for 30 s) (A)
- Intralesional antimonials: 1–5 ml per session every 3–7 days (1–5 infiltrations) (B)

**Systemic**
- *L. mexicana*
  - Ketoconazole: adult dose, 600 mg oral daily for 28 days (B)
  - Miltefosine: 2.5 mg/kg per day orally for 28 days (B)

- *L. guyanensis* and *L. panamensis*
  - Pentamidine isethionate, IM or brief infusions of 4 mg salt/kg per dose every other day for 3 doses (C)*
  - Pentavalent antimonials: 20 mg Sb5+/kg per day for 20 days (C)*
  - Miltefosine: 2.5 mg/kg per day orally for 28 days (B)

- *L. braziliensis*
  - Pentavalent antimonials: 20 mg Sb5+/kg per day for 20 days (A)
  - Amphotericin B deoxycholate: 0.7 mg/kg per day, by infusion, for 25–30 doses
  - AmBisome 2–3 mg/kg per day, by infusion, up to 20–40 mg/kg total dose (C)

- *L. amazonensis, L. peruviana and L. venezuelensis*
  - Pentavalent antimonials: 20 mg Sb5+/kg per day for 20 days

#### Recommended treatment regimens for OW CL

**No antileishmanial treatment**

**Local therapy**
- *L. major*
  - 15% paromomycin / 12% MBCl twice daily for 20 days (A)
  - Intrallesional antimonials, 1–5 ml per session plus cryotherapy (liquid nitrogen both every 3–7 days (1–5 sessions) (A)
  - Thermotherapy, 1–2 sessions with localized heat (50 °C for 30 s) (A)
  - Intralvesional antimonials or cryotherapy independently, as above (D)

- *L. tropica, L. aethiopica* and *L. infantum*
  - 15% paromomycin / 12% MBCl as above (D)
  - Intralvesional antimonials plus cryotherapy, as above (D)
  - Thermotherapy, as above (A)
  - Intralvesional antimonials, alone, as above (B)
  - Cryotherapy, alone, as above (C)

**Systemic therapy**
- *L. major*
  - Fluconazole, 200 mg oral daily for 6 weeks (A)
  - Antimonials, 20 mg Sb5+/kg per day for 10–20 days (D)
  - Antimonials, 20 mg Sb5+/kg per day + pentoxyfylline, 400 mg three times a day for 10–20 days (A)

- *L. tropica and L. infantum*
  - Antimonials, 20 mg Sb5+/kg per day for 10–20 days (D)
  - Antimonials, 15–20 mg Sb5+/kg per day for 15 days plus oral allopurinol 20 mg/kg for 30 days, to treat leishmaniasis recidivans caused by *L. tropica*

- *L. aethiopica*
  - Antimonials 20 mg Sb5+/kg per day + paromomycin, 15 mg (11 mg base)/ kg per day IM for 60 days or longer to treat diffuse cutaneous leishmaniasis
Challenges in treatment development

• CL is not fatal, hence very few efforts on drug screening.
• Interpretation of results from some tests, such as the *in vitro* intracellular amastigote model, is complicated given:
  • variable rate of infectivity
  • type of macrophage host cell used,
  • intrinsic susceptibility of laboratory strains and clinical isolates.
• *In vivo* experimental models for CL do not accurately reproduce the biological responses that occur in humans → not good translation of results from animal model to humans.
• Parasite and patient genetic diversity.
Consequences of lack of treatment development

- There are no examples of a pre-clinical testing strategy that has lead to formal clinical development of anti-CL agents. Drugs currently in use for CL treatment were repurposed or developed for other diseases.
- Current treatments for CL are poorly justified and have sub-optimal effectiveness.
- A wide variety of treatment modalities has been used and reported for CL, but none has been shown to be universally effective.
- Few clinical trials have been properly designed and reported.

CL is a most neglected disease, Neglected populations

Objective: To achieve short, safe, non-invasive, efficacious, affordable and field-friendly treatments for CL, mainly caused by *L. tropica* and *L. braziliensis*.
Current developments

**Topical**
- WR 279,396 (paromomycin and gentamicin)
- Anfotericin B 3% (Anfoleish)
- Meglumine Antimonate Ointment
- Liposomal formulations

**Systemic**
- Fexinidazole
- Edelfosine (D121)

**Combinations**
- Pentoxifylline + SAG
- Nitric Oxide Releasing Patch + SAG
- CpG D35 + Antiparasitic drug
Summary

- Treatment of CL is not a simple task
- Treatment has long depended on antiquated drugs that would be considered far too toxic for introduction under modern registration systems.
- Even though progress has been made for VL treatment, for CL it seems that what is currently available will probably represent almost the entire therapeutic arsenal for the coming years.
- Although basic research will continue the current challenge is to make better use of what is already available.
“We must accept finite disappointment, but we must never lose infinite hope.”

Martin Luther King Jr.