Leprosy

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Introduction

- Leprosy is associated with stigma
Introduction

Leprosy in the Old Testament is not one disease

- Original Hebrew “tsara’ath” – group of diseases
- Translated to “lepra” in Greek – 100 BC
- 1384 Wycliffe translated “lepra” to “leprosy” a disease seen in Europe at that time and described as a “unholy and loathsome condition”
One of the leading causes of permanent physical disability in the world

Afflicts individuals in their most productive stage of life

Multi-drug therapy (MDT) can eliminate leprosy as a public health problem (prevalence < 1/10,000)

MDT can also bring about cure without disability
## Global Situation

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Registered cases 2000 (rate/10,000)</th>
<th>New cases detected 1999 (rate/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>64490 (1.0)</td>
<td>55635 (8.6)</td>
</tr>
<tr>
<td>Americas</td>
<td>90447 (1.1)</td>
<td>45599 (5.7)</td>
</tr>
<tr>
<td>SE Asia</td>
<td>574924 (3.8)</td>
<td>621620 (41.3)</td>
</tr>
<tr>
<td>E Mediterranean</td>
<td>8785 (0.2)</td>
<td>5757 (1.2)</td>
</tr>
<tr>
<td>W Pacific</td>
<td>13771 (0.1)</td>
<td>9501 (0.6)</td>
</tr>
<tr>
<td>Europe</td>
<td>846 (negligible)</td>
<td>172 (negligible)</td>
</tr>
<tr>
<td>Total</td>
<td>753263 (1.25)</td>
<td>738284 (12.3)</td>
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</tbody>
</table>

Manson’s Tropical Medicine, 21st edition, pp1065
<table>
<thead>
<tr>
<th>Country</th>
<th>Registered cases 2000</th>
<th>Prevalence / 10000</th>
<th>New cases during 1999</th>
<th>Detection rate / 100000</th>
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</thead>
<tbody>
<tr>
<td>India</td>
<td>495073</td>
<td>5.0</td>
<td>537956</td>
<td>54.3</td>
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<tr>
<td>Brazil</td>
<td>78068</td>
<td>4.3</td>
<td>42055</td>
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<tr>
<td>Myanmar</td>
<td>28404</td>
<td>5.9</td>
<td>30479</td>
<td>62.9</td>
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<td>Indonesia</td>
<td>23156</td>
<td>1.1</td>
<td>17477</td>
<td>8.3</td>
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<tr>
<td>Nepal</td>
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<td>18693</td>
<td>78.7</td>
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<tr>
<td>Madagascar</td>
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<td>4.7</td>
<td>8704</td>
<td>51.6</td>
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<tr>
<td>Ethiopia</td>
<td>7764</td>
<td>1.3</td>
<td>4457</td>
<td>7.4</td>
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<tr>
<td>Mozambique</td>
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<td>3.9</td>
<td>5488</td>
<td>28.7</td>
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<tr>
<td>D.R. Congo</td>
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<td>1.0</td>
<td>4221</td>
<td>8.6</td>
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<tr>
<td>Tanzania</td>
<td>4701</td>
<td>1.4</td>
<td>5081</td>
<td>15.4</td>
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<tr>
<td>Guinea</td>
<td>1559</td>
<td>2.0</td>
<td>2475</td>
<td>32.0</td>
</tr>
<tr>
<td>Total</td>
<td>672596</td>
<td>4.1</td>
<td>677086</td>
<td>41.7</td>
</tr>
</tbody>
</table>
Organism

- Mycobacterium leprae – acid fast bacillus
- Primarily found in masses within macrophages
- Intra and extra-cellular globi
Leprosy bacilli
Transmission

► Two portals of exit
  ▪ Skin
  ▪ Nasal mucosa
    ► Majority of lepromatous patients have bacilli in nasal secretions from blowing the nose
    ► Can yield as many as 10 million viable organisms per day

► MDT renders a person non-infective after a few doses
Viability of M. leprae

- 36 hours to 9 days
- Contaminated fomites and clothing could be a source of infection
Portal of Entry

- Skin
- Upper respiratory tract – most likely route
- Others?
  - Breast Milk
  - Placental
In vitro culture

► No substantiated in vitro culture of the bacillus
In vivo culture

- Mouse footpad culture is the standard
- Use of the footpad culture method
  - Culture diagnosis of patients
  - Minimum concentration of treatment drugs
  - Sensitivity to new drugs
  - Drug resistance in patients
Nine banded Armadillo

- The armadillo can be infected with leprosy
- Has a primitive immune system and low body temperature
- IV inoculation produces disseminated disease
- Main source of leprosy research
Other animals

- Chimpanzee in Sierra Leone
- Mangabey monkey in West Africa
M. leprae has the longest doubling time of all known bacteria – extreme case of reductive evolution

Less than half the genome contains functional genes eliminating many important metabolic activities

There are 1500 genes common to TB and M leprae

TB and M leprae derived from a common ancestor and likely had gene pools of similar size

Many of the genes of M leprae have been lost.
Epidemiology

- Transmission = close contact with leprosy patients
  - Cebu – 6.2/1000/year
  - South India – 55.8/1000/year
- Upper respiratory route most likely
- Other factors for clinical expression:
  - Genetics
  - Route of entry
  - Malnutrition
  - Prior exposure to other mycobacterial organisms
Leprosy an Immune Disease

![Graph showing immune response in different stages of leprosy and healthy individuals.]

- **CMI to ML**
- **No. Org**
- **Antibody**
Epidemiology - Age at onset

- Mainly young adults
- Range of infections from 3 weeks old to 141 years old
Epidemiology - Gender

- Males affected more than females – 2:1 ratio
- In many parts of Africa there is an equal gender distribution
- In Uganda, Nigeria, Malawi, Gambia, Burkina Faso, Zambia, Thailand, and Japan there is a female predominance
Epidemiology - Incubation period

- Few weeks to 30 years +
- The average – 3-5 years
Epidemiology – Sub Clinical Infection

- Sub-clinical infection is far more common than overt disease.
- The factors influencing the onset of disease may be different from those associated with infection.
Epidemiology – Household contacts

- Household contacts of leprosy patients are at greater risk of developing leprosy disease vs non-household contacts

- Household contacts contribute only a limited proportion of all new cases
Epidemiology - HIV

- No association of HIV and leprosy
Epidemiology - BCG

- BCG seems to provide some protection against leprosy
  - Field trials – Malawi, Myanmar, Papua New Guinea, Uganda, Venezuela, India
  - Protective efficacy – 20-30% Myanmar, 50% Venezuela, 80% in Uganda
  - Greater effect if vaccinated < 15 yo
  - Booster doses seems to increase protection
  - Addition of killed M leprae organisms does not increase protection
  - Use of BCG may be contributing to the decline of leprosy worldwide
Epidemiology - Disability

- 2 million worldwide with leprosy disability
- Men
- Multibacillary forms
- Age
- Duration of disease
- Significantly reduced with MDT
Epidemiology - Lepromin

- This skin test is still used as an indicator of CMI response to the organism.
- Limited use in diagnosis or indicator of protective immunity.
- Use killed organisms:
  - Fernandez reaction – 48 hours
  - Mitsuda
    - Delayed CMI response (3-4 weeks)
    - $\geq 5$ mm – tuberculoid
    - 3-5 mm – borderline
    - 0-2 mm - lepromatous
Epidemiology - Mortality

- Rarely the immediate cause of death
- Indian and Philippines lepromatous patients had a 4X and non-lepromatous patients have a 2X increased mortality vs the general population
Clinical - General

- Majority of people significantly exposed experience infection but develop no signs or symptoms
- Onset is quite variable and progression is usually insidious
  - Skin lesions – hypopigmented or erythematous patch with anesthesia, single, multiple or diffuse
  - Spontaneous healing is common in childhood and some communities
  - Unlike TB there is an absence of toxicity with large numbers of organisms present
  - At any stage sudden exanthems may be seen associated with fever
  - Chronic onset is so gradual and insidious that it is usually far advanced on presentation
  - Acute onset (less common) presents often with multiple lesions that spread rapidly and contain numerous bacilli, often associated with another stressor
Case Definition

- Hypopigmented or erythematous skin lesion(s) associated with loss of sensation
- Involvement of the peripheral nerves with loss of sensation and weakness of the muscles of the hands, feet or face
- Positive skin smear for leprosy bacilli

Must have at least one of the above to meet the case definition
# Ridley-Jopling Classification

<table>
<thead>
<tr>
<th>Sign or Test</th>
<th>Type of Leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT</td>
</tr>
<tr>
<td>No of lesions</td>
<td>Usually single</td>
</tr>
<tr>
<td>Size of lesions</td>
<td>Variable</td>
</tr>
<tr>
<td>Surface of lesions</td>
<td>Very dry, scaly</td>
</tr>
<tr>
<td>Hair in lesions</td>
<td>Absent</td>
</tr>
<tr>
<td>Sensation</td>
<td>Completely lost</td>
</tr>
<tr>
<td>AFB in smears</td>
<td>None</td>
</tr>
<tr>
<td>Nasal AFB</td>
<td>None</td>
</tr>
<tr>
<td>Lepromin test</td>
<td>+++</td>
</tr>
</tbody>
</table>
Fite stain of the biopsy specimen under oil immersion at 100x magnification shows numerous acid-fast bacilli and that organisms have infiltrated a nerve. Note the foamy histiocyte in the image at right.

Hematoxylin-eosin stain of the biopsy specimen under oil immersion at 100x magnification reveals a superficial and mid-perivascular infiltrate dominated by lymphocytes without spongiosis.
Leprosy an Immune Disease
Lepromatous Leprosy

► Wide dissemination
  - Skin
  - Nerves
  - Reticuloendothelial system
  - Eyes
  - Testes
  - Bones
  - Mucous membranes
  - Mouth
  - Nose
  - Phargnx
  - Trachea
Lepromatous Leprosy - Skin

- Multiple, symmetric macules (flat), plaques (elevated), papules and nodules
- Macules are usually the first seen most commonly seen on the face, buttocks and extremities
- Macules may be erythematous in light skin and faintly hypopigmented in dark skin
- Plaques are elevated and do not appear on the palms and soles
- Papules and nodules occur as the disease advances and favor the face, ears and buttocks
- Leonine facies – enhanced wrinkles, loss of eyebrows
- Nodules and plaques may ulcerate on legs when associated with lymphedema
- Pure Diffuse – skin of the whole body becomes infiltrated and resembles scleroderma, also can be associated with Lucio’s phenomena
Skin slit
Lepromatous Leprosy – Nerve Involvement

► The nerves are not involved without the skin
► Nerves are damaged later in LL
► Sensory loss is predominant
► Nerve thickening is symmetric (great auricular, supraclavicular, ulnar, antebrachial in the forearm, radial and median at the wrist, femoral cutaneous, common peroneals, superficial peroneal at the front of the ankles, posterior tibial below the internal malleolus)
► Sensory disturbance – paresthesia, hyperesthesiae, hyperalgesia, anesthesia (light touch, temperature, pain)
Other tissues involved with LL

- Nails of fingers and toes – dry, lusterless, narrowed, longitudinally ridged

- Mucous membranes
  - Nose – discharge, blocked airway, swollen mucosa, nodules / ulcers on the septum, septal perforation (saddle nose)
  - Mouth – nodules / ulcerations on lips, tongue, palate
  - Larynx – nodules / ulcerations, altered voice, stidor
  - Glottis – edema, obstruction
Other tissues involved with LL

- **Eye**
  - Corneal changes
  - **Iridocyclitis**
    - Acute
    - Insidious
  - Cataracts
Other tissues involved with LL

► Musculoskeletal system

  ▪ Skull, arms and legs
  ▪ Multiple factors
    ► Bacilli invading bones – cysts and perostitis
    ► Neurotrophic changes – localized to the phalanges
    ► Repeat trauma
    ► Disuse atrophy
    ► Secondary infections
    ► Generalized osteoporosis
Other tissues involved with LL

- Reticuloendothelial system (RES)
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Lymphedema of the lower legs - elephantiasis

- Testes – testicular atrophy

- Kidneys – glomerulonephritis, interstitial nephritis, pyelonephritis, renal amyloidosis
Leprosy an Immune Disease

![Graph showing immune response in different leprosy stages and healthy individuals.](image-url)
Tuberculoid Leprosy

► Good immune response
► May be neural or neural and dermal
► Localized
Tuberculoid Leprosy

► Neural Disease

- Thickened nerves
- Sensory and motor involvement
- Motor changes affect the face, intrinsic muscles of the hand and dorsiflexors of the feet
- Abscesses along affected nerves can be seen
- Eye can be involved due to damage to the facial nerve
Tuberculoid Leprosy

► Dermal Disease
  ▪ Macules and plaques
  ▪ Asymmetric
  ▪ Face, extensor surfaces of limbs, back, buttocks
Borderline Leprosy

- Not strictly localized like TT or as widespread as LL
- Nerve involvement can always be demonstrated and often preceded skin lesions
- Nerves are thickened and show sensory and motor involvement
Indeterminate Leprosy

► Early phase and has not yet committed to either TT or LL
► Single macule, uncharacteristic histology, absence of bacilli
Antileprosy Medications

► Standard
- Rifampicin (rifampin, rifadin, rimactane)
- Clofazamine
- Dapsone (4,4’ diaminodiphenylsulfone)

► Special situations
- Ofloxacin
- Minocycline
- Clarithromycin
Standard MDT regimens

► Multibacillary – Rx for 12 months (US 1-3 years)
  - Rifampicin: 600 mg once / month, supervised
  - Dapsone: 100 mg once / month, self administered
  - Clofazamine: 300 mg once / month, supervised + 50 mg daily, self administered

► Paucibacillary – Rx for 6 months (US 1 year)
  - Rifampicin: 600 mg once / month, supervised
  - Dapsone: 100 mg daily, self administered

Pregnancy and Lactation – Leprosy is exacerbated in pregnancy therefore the above regimens are recommended unchanged for pregnancy and lactation. Some of the medications are excreted in small quantities in breast milk but no adverse reactions have been noted.

HIV patients respond to standard MDT

55
Pediatric Doses

- Dapsone – 1 mg /kg
- Rifampin – 10 mg / kg
- Clofazamine – 1 mg / kg
Special Situations

► Single lesion paucibacillary leprosy
  - Single dose therapy (ROM)
    ▶ Rifampicin 600 mg
    ▶ Ofloxacin 400 mg
    ▶ Minocycline 100 mg
    ▶ Marginally less effective than standard MDT for paucibacillary disease

► Can’t take Rifampicin
  - Treat for 24 months
    ▶ Clofazamine 50 mg / day +
    ▶ Two of the following / day (Ofloxacin 100 mg, Minocycline 100 mg, or Clarithromycin 500 mg) for 6 months then
    ▶ Daily Clofazamine 50 mg + either Minocycline 100 mg or Ofloxacin 400 mg for 18 months
Special Situations

► Multibacillary patients Refusing Clofazamine
  - Standard MDT but replacing Clofazamine by Ofloxacin 400 mg daily or Minocycline 100 mg daily for 12 months
  - 24 month regimen (ROM) of Rifamipcin 600 mg / month, Ofloxacin 400 mg / month and Minocycline 100 mg / month
Special Situations

► Can’t take Dapsone

- With multibacillary disease just stop the Dapsone and continue the other meds (rifampicin and clofazamine)
- With paucibacillary disease substitute clofazamine for dapsone
Reactions

► Lepra reactions – immune mediated inflammation
► 5% of PB and 20% of MB patients
► Two major types
  ▪ Reversal (type 1)
  ▪ ENL (erythema nodosum leprosum) (type 2)
► ENL less common with MDT
Reversal Type 1

- Lesion changes – Erythema, edema, pain, tenderness over nerves
- High risk of nerve damage
- Treat – Steroids (1 mg / kg / day, max 40-60 mg of prednisolone)
- Taper off steroids over a 12 week period
ENL type 2

- Varies in severity duration and organ involvement
- Rapid onset of erythematous nodules, fever, joint inflammation, iridocyclitis, ulceration of the skin, glomerulonephritis and amyloidosis
- Mild ENL Rx – Aspirin
- Severe ENL with neuritis – Rx with prednisolone as for Type 1 reactions
- Clofazamine may be useful when withdrawing steroids (dose 300 mg / day divided doses)
- Iridocyclitis – add topical steroids to regimen
Lepra Reaction – Program Recommendations

► Patients taught to recognize Lepra reactions and report promptly
► Clinicians able to diagnose and promptly treat reactions
► Adequate stocks of medications to treat reactions
► Continue MDT without interruption during a lepra reaction
Relapse

- 0.1% relapse rate
- All *M. leprae* from relapse patients remain susceptible to rifampicin and clofazamine and respond favorably to a second course of MDT
Strategies for eliminating Leprosy as a public health problem

- Identification of endemic districts
- MDT services integrated into general health facilities
- Monitoring the elimination at the district level
- Promoting community action
- Social marketing / advocacy
- Remotivating the research community
- Prevention of disabilities and rehabilitation