Tuberculosis
Etiology, Epidemiology, Pathogenesis, Clinical Manifestation

General Medicine
English Learning Programme
Phthisiology, Lecture #1
3200-2800 BC - Ancient Indians: „Consumption“
400 BC - Hippocrates: „Phthisis“
19th century - Peak incidence in Western Europe and North America
1882 - M. tuberculosis identified by Koch
1920 - „sanatorium regimen“, collapse therapy, thoracoplasty
1960 - Chemotherapy
Mycobacteria genus

- over 40 species (mostly saprophytes)
- tuberculosis complex:
  - M. tuberculosis
  - M. bovis (reactivation disease in elderly people)
  - M. africanum
  - M. microti - not pathogenic except under special circumstances
  - BCG - not pathogenic except under special circumstances
Bacteriology

- acid (alcohol, alkalis) fastness
- slow rate of growth
- sensitive to heat and UV irradiation
- nonmotile
- nonsporulating
1/3 of the global world population is infected
7-9 million new cases / year
Annual mortality 1.3 million people (2012)
Mortality without specific therapy: 70% of smear-positive patients within 10 years
90 million new cases worldwide in the 1990s
30 million deaths worldwide in the 1990s
2000-2020 one billion people will be newly infected
2000-2020 200 million people will get sick
2000-2020 35 million people will die
1 new infection every second
9 mil. new cases (2013), 1.1 mil. of them (13%) HIV+, 6.1 mil. reported to WHO
Global prevalence, 1990–2012
TB notification rates 2013

Figure 1.15: Tuberculosis notification rates, by country, 2007

Notified TB cases (new and relapse) per 100,000 population:
- 0-24
- 25-49
- 50-99
- ≥100
- No report
Global mortality, 1990–2012

- Deaths [thousands]
- Mortality

The diagram shows a downward trend in both deaths and mortality from 1990 to 2012.
FIGURE 2.12
Estimated TB mortality rates excluding TB deaths among HIV-positive people, 2012
## The leading causes of mortality in the world 2004

<table>
<thead>
<tr>
<th></th>
<th>mil.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ischaemic heart disease</td>
<td>7.2</td>
<td>12.2</td>
</tr>
<tr>
<td>2. Cerebrovascular disease</td>
<td>5.7</td>
<td>9.7</td>
</tr>
<tr>
<td>3. Lower respiratory infections</td>
<td>4.2</td>
<td>7.1</td>
</tr>
<tr>
<td>4. COPD</td>
<td>3.0</td>
<td>5.1</td>
</tr>
<tr>
<td>5. Diarrhoeal diseases</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>6. HIV/AIDS</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>7. Tuberculosis</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>8. Trachea, bronchus, lung cancers</td>
<td>1.3</td>
<td>2.3</td>
</tr>
<tr>
<td>9. Road traffic accidents</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>10. Prematurity and low birth weight</td>
<td>1.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>
The leading causes of death and of premature death, world, 1990

<table>
<thead>
<tr>
<th>Causes</th>
<th>Percent of total deaths or YLLs</th>
</tr>
</thead>
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<td>Ischaemic heart disease</td>
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<td>Lower respiratory infections</td>
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<td>Diarrhoeal diseases</td>
<td></td>
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<tr>
<td>Conditions arising during the perinatal period</td>
<td></td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td></td>
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<tr>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td></td>
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<td>Road traffic accidents</td>
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<tr>
<td>Trachea, bronchus and lung cancers</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td></td>
</tr>
</tbody>
</table>
The relationship between the rank order of causes of global ill-health when measured using deaths alone or total disease burden, 1990.
Estimated TB prevalence by WHO region

- AFR
- AMR
- EMR
- EUR
- SEAR
- WPR
- World

Prevalence (all forms per 100,000)

- 1990
- 2005
- Target
# Risk of the infection

## Exposure
- Living in the household of a tuberculosis case
- Immigration from an endemic area (Asia, Latin America)
- Exposure in congregate living facilities (jails, shelters, health care facilities)
- Older age
- Residence in higher incidence location (inner cities)

## Susceptibility
- HIV+ & PPD > 5 mm
- Drug users
- Close contacts of person known or suspected to have TB, sharing the same household or other enclosed environment & PPD > 5 mm
- Documented recent converters (PPD increase > 10 mm within 2 years for those under age 35 or > 15 mm - 35 years old and over)
- Medical risk factors (+PPD > 10 mm):
  - silicosis
  - weight of 10% or more below ideal body weight
  - chronic renal failure
  - diabetes mellitus
  - prolonged corticosteroid therapy
  - Persons from areas with high TB prevalence < 35 years old + PPD > 10 mm
  - Any skin test reactor less than 15 years old (PPD > 10 mm)
## Risk of the infection

<table>
<thead>
<tr>
<th>Group</th>
<th>Annual risk of TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>3-10%</td>
</tr>
<tr>
<td>PPD Converters</td>
<td>2-5%</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>2-4%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.3%</td>
</tr>
<tr>
<td>No risk factor</td>
<td>0.01-0.1%</td>
</tr>
</tbody>
</table>
Estimated HIV prevalence in new and relapse TB cases 2013
Proportion of HIV-attributed Tuberculosis Cases in the World (Estimates for 1990-2012)

Estimated Cases [Millions]

1990: 7.5 (4.2%)
1995: 8.8 (8.4%)
2000: 10.2 (13.9%)
2011: 7.6 (12.6%)

Not related to HIV
HIV-attributable
FIGURE 7.1  Number of TB patients with known HIV status, 2004–2011

TB patients (thousands)

HIV status
- Positive
- Negative
Natural History of Tuberculosis Infection

- **Exposure**
  - TB Infection (30%)
  - No TB Infection (70%)

  **TB Infection (30%)**
  - Primary TB (5%)
    - HIV+ (~40%)
  - +PPD (95%)
    - HIV+ (~60%)

  **No TB Infection (70%)**
  - Reactivation TB (5%)
    - HIV+ (2-10%/year)

  - Lifelong Containment (90%)
    - HIV+ (?)

Pathogenesis
Primary infection

- in patients without specific immunity
- phagocytosis by alveolar macrophages
- primary lesion (Ghon focus) - mid or lower lung zones
- marked tendency to central liquefaction and cellular breakdown
- spread through lymphatic to regional lymph nodes - marked reaction
- spread into blood stream - possible settling throughout body
Primary infection

- Mannose receptor
- Lipoarabinomannan
- Phagosome
- Complement receptor
- Lysosome

- inhibition of Ca²⁺ signals
- Blockage of recruitment and assembly of fusion mediating proteins

Pathogenesis

- Transport to lymph nodes
- Dissemination by blood stream
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**Pathogenesis**

- **Primary infection**
  - Mannose receptor
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**Inhibition**
- Inhibition of Ca$^{2+}$ signals
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**Transport**
- Transport to lymph nodes
- Dissemination by blood stream

**Cellular Response**
- AM
- Lysosome
- Phagosome

**Cell Types**
- CD4+$^+$
- CD8+$^+$
- CD4-8-$^-$
- APC
- Th1
- IFNγ

**Granuloma Formation**
- Epitheloid cell
- Granuloma formation
- Killing of intracellular mycobacteria (NO, NO2, HNO3)

**Killing Mechanisms**
- Fas dependent
- Fas independent, granule dependent

**Acidic Environment**
- Caseating granulomas
- Acidic environment
- Stop growth of MTB
Primary infection

- the younger the age at which the primary infection occurs, the more likely it is to be associated with significant disease, miliary TB and TB meningitis
- after 3 weeks - 3 months - specific immunity (tuberculin skin test conversion)
- healing of the primary lesion (scar, calcification)
Primary infection - complications

- Progressive disease (cavitation)
- Tuberculoma
- Atelectasis (bronchial compression)
- Enlarged lymph nodes
- Pleural involvement
- Hematogenous spread (miliary TB)
Post-primary disease

- 3-5 years after primary infection
- consequence of hematogenous primary spread (reinfection???)
- site: lung, bone, lymph nodes
- greater cellular response
- less tendency to caseation
- less response in the regional lymph nodes
- less common hematogenous spread
- more prominent fibrosis
- bronchial involvement („asymptomatic“ bronchiectasis)
- at the start – appearance of a small irregular „pneumonia“
- clinical course – different (according immune-status)
Symptoms of respiratory tract involvement

- Cough
- Sputum (mucoid, mucopurulent)
- Haemoptysis
- Chest pain (pleural involvement, mediastinal lymph nodes enlargement)
General symptoms

- Fever (active, progressive disease, inverse temperature chart)
- Night sweats
- Loss of appetite, weight loss
- Other symptoms: amenorhea, stool disturbances, hoarseness, arrhymias, erythema nodosum, phlyctenular conjunctivitis...