TUBERCULOSIS

GENERAL
Tuberculosis (TB) kills 1,700,000 annually worldwide.

"The Captain of all the men of death that came to take him away was the consumption, for it was that which brought him down to the grave."  
John Bunyan, 1680

Famous victims in their intellectual prime:  
Chopin, Paganini, Thoreau, Keats, Elizabeth Browning, Brontës

One-third of the world’s population have been infected.

Synergy with the HIV/AIDS pandemic.

Mounting problems with multi-drug resistant tuberculosis (MDRTB)

Before antibiotics, the case-fatality rates for tuberculosis were 40% - 60%.

30 million active cases of disease.  
8 million new cases of tuberculosis appear each year.  
  95% are in developing countries.  
  5% are in industrialized countries.  
  Highest incidence in Africa.

Factors contributing to spread include  
  Ignorance  
  Poverty  
  Overcrowding  
  Poor hygiene  
  War and economic depressions

No useful serologic test for TB.  
New T-cell assays promising.

Two closely related agents cause similar disease.  
Mycobacterium tuberculosis (lung)  
Mycobacterium bovis (gut)
CLINICAL FEATURES

TB is a slow progressive disease.
The organism elicits a granulomatous response.
Characterized by high infectivity and low virulence.

Two patterns of disease
- Primary tuberculosis
- Reactivation tuberculosis

Primary TB
- Usually pulmonary (starts at periphery or mid-zone of lung)
- Tubercle bacilli in alveoli are engulfed by macrophages.
- Macrophages carry infection to hilar lymph nodes.
- Multiplication of bacilli proceeds with a minor inflammatory reaction.
- Bacilli may travel to other tissues via lymphatic circulation.
  - Liver
  - Spleen
  - Kidney
  - Bone
  - Brain and meninges
  - Lung apices

Symptoms are usually absent to minimal (mild flu-like illness).
Cell-mediated immunity develops after 2 - 6 weeks of infection.
Formation of microscopic granulomas
  - Multi-nucleated giant cells and cell necrosis (central area)
  - Lymphocytes (peripheral area)

Most primary infections are controlled by host immune response
  - Mycobacterial multiplication stops in the granulomas
  - Most organisms slowly die
  - Granulomas scar (fibrosis) and calcify
  - In some granulomas, mycobacteria can remain viable for years
  - Basis for reactivation

5% of primary infections progress
  - Dissemination with active milliary disease
  - Necrotic tubercle eroding into small blood vessel
Reactivation TB

-10% develop reactivation sometime during lifetime.
In Western countries, usually occurs after age 50 years.
In developing countries, less defined age pattern.
Reactivation increases with
  - Malnutrition
  - Alcoholism
  - Diabetes
  - Older age
  - Severe stress (loss of spouse)
  - HIV/AIDS (reactivation rate increased by 200 - 300 fold)

Reactivation site
  - Often in the lung apex
  - Higher oxygen concentration
  - Less blood perfusion
  - Less lymphatic drainage

Lesions are slow spreading
  - Coalescing tubercles
  - Enlarging region of tissue necrosis
  - Small blood vessels eroded (blood in sputum)
  - Pulmonary cavities

Symptoms or reactivation
  - Chronic fevers
  - Weight loss
  - Night sweats
  - Productive coughs with blood

Dissemination to other organs (especially with HIV/AIDS patients)
  - Kidneys
  - Bones
  - Lymph nodes
  - Brain and meninges
  - Bone marrow
  - Bowel
EPIDEMIOLOGY
Transmission modes
   #1 Respiratory (breathing droplet nuclei)
   #2 Gastrointestinal (eating contaminated milk or meat)
   #3 Skin (direct contact)

TB’s ID-50 is undefined
   Infection is a stochastic process
   Single cough produces 1,000,000 infectious droplet nuclei
   No clear threshold of organisms required to produce infection.

Factors for acquiring infection
   Number of bacilli in sputum
   Frequency and efficiency of coughs
   Closeness of contact
   Degree of ventilation in contact area

Industrialized countries
   80% of cases are in people ≥50 years
   Most cases are due to reactivation.
   Few cases are due to recent exposure.

Developing countries
   Infection involves all age groups.
   75% of cases are in people <50 years
   80% of impact on economically productive years.
   26% of avoidable deaths.

Age < 15 years
   1,300,000 cases
   450,000 deaths
### Epidemiological patterns of tuberculosis
#### Annual Risk of Infection

<table>
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<th>Area</th>
<th>Current level (%)</th>
<th>Annual decline (%)</th>
<th>Health Resources</th>
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<td>0.1 - 0.01</td>
<td>&gt;10</td>
<td>Excellent</td>
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<td>Latin America</td>
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<tr>
<td>Middle Income</td>
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<td>1.0 - 2.5</td>
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<td>Indian Subcontinent</td>
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United States (Case Study)

Early 1980 PPD-positive
- 5% overall population
- 1% children
Higher among nonwhite and urban poor
Most cases were in people ≥50 years (reactivation)
Steady decline stopped in 1985

From 1985 - 1992
- 20% increase in active cases attributed to Immigrants
- Intravenous drug users
  - 6 - 7% annual conversion rates
- HIV/AIDS cases
  - Reactivation rates increased by 200 - 300 fold
  - 8% annual reactivation rate
- Single-source outbreaks
  - Classrooms
  - Homeless shelters
  - Nursing homes
  - Hospitals
  - Prisons

Impact of HIV infection
- Increases risk of reactivation disease
- Increases risk of disseminated infection

Worldwide Comparisons
In 1992
- 10 - 12 million HIV infected adults worldwide
- 3.0 million HIV/TB co-infections worldwide.
- 2.4 million HIV/TB co-infections in Sub-Saharan Africa alone.

In 2000
- 30 - 50 million HIV infected adults worldwide
- 75% of HIV transmissions occurring where TB is common
PATHOGEN’S FEATURES

Characteristics

*Mycobacterium tuberculosis*
*Mycobacterium bovis*
Gram positive bacilli
Slim rod-shaped organism
  - 0.2 - 0.4 um diameter
  - 2 - 10 um length
Non-motile
Does not form spores
Strictly aerobic
Does not produce exotoxin or endotoxin

Slow growing at 37C
Does not grow at room temperature
Mean generation time of 12 - 24 hours
Colonies appear after 3 - 6 weeks of incubation
Organisms require rich media
Growth enhanced by 5 - 10% CO2
Heat sensitive (killed by pasteurization at 30 minute and 62C)

Cell Wall

Unique glycoprotein
  - N-glycolymuramic acid
  - Most bacteria contain N-acetylMuramic acid
Hydrophobic cell wall
  - 60% lipid content
  - Causes bacteria to clump which inhibits permeability of nutrients
  - Grows more slowly than most other human pathogenic bacteria
Acid-fast and alcohol-fast bacilli (AFB)
  - Difficult to stain but once stained difficult to decolorize
  - Cell wall resists decolorization with 3% HCl and 95% ETOH
  - Distinguishing feature of Mycobacteria

Pathogenicity

No single virulence gene has been identified.
The basis for virulence is not clear.
Disease results from delayed-type hypersensitivity reactions to proteins
Purified protein derivative (PPD)
Immunity
Differences in immunity reflect extent of exposure of forebears
Recently exposed populations
Native Americans and Eskimos
Higher morbidity
Higher mortality

Diagnosis
Clinical symptoms
Chest X-rays
Skin tests
Sputum smears
Cultures

Delayed-type hypersensitivity to proteins
Purified protein derivative (PPD)
Score reactions 48 - 72 hours later

Positive PPD
Indicates prior exposure and immune reaction
*Mycobacterium tuberculosis*
*Mycobacterium bovis*

Negative PPD
No previous exposures
Pre-hypersensitive stage of infection
Loss of sensitivity over time
Loss of sensitivity (anergy)
AIDS
Steroids or immune suppressive drugs
Measles

T-cell-based assays (ELISPOT)
Some promise

Smears
Sputum: 65% culture-positive samples are smear-positive
Contamination by other mycobacteria may yield false-positive results
PCR probes are being developed and used but are expensive.
Cultures
Typical samples include
- Cerebrospinal fluid
- Bone marrow
- Pleural fluid
- Sputum

Treat with (alkali, acid, detergents) to kill normal flora but not TB
Solid media requires 3 weeks or longer to show visible colonies
Liquid media cuts detection times in half (14C-labeled palmitic acid)

Biochemical tests — identify the specific organism
- DNA/RNA probes
- Gas chromatography

Drug susceptibility tests require 1 - 2 weeks

**Drug therapies**
Most countries do not have ways to monitor treatment outcomes.
Patients are non-infectious after 1 - 2 weeks of therapy

First-line drugs
- ISONIAZID
- ETHAMBUTOL
- RIFAMPIN
- PYRAZINAMIDE
- STREPTOTYMCIN

Second-line drugs
- PARA-AMINOSALICYLIC ACID
- ETHIONAMIDE
- CYCLOSERINE
- FLUROQUINOLINES (CIPRO)
- KANAMYCIN

Typical therapies
- Start with 2 - 4 agents (before susceptibility testing)
  - ISONIAZID + RIFAMPIN (9 months)
  - ISONIAZID + RIFAMPIN + PYRAZINAMIDE (6 months)
Typical Outcomes
< 50% patients are cured.
25% of patients do not complete 6 months of treatment within one year

Model Outcomes
≥ 80% in Malawi, Mozambique, Nicaragua, Tanzania
Feasible to achieve 90% cure rates with existing technology and drugs

Drug Prophylaxis
ISONIAZID
Usually used as single agent
Indications
Radiological evidence of active primary complex
Close contact of infectious case
Recent PPD conversion
Immunosuppression and PPD-positive

Drug Resistance
Mutation
1 per $10^7$ to $10^{10}$ organisms
Body burdens $\geq 10^{10}$ organisms
Resistance develops when one drug is used for treatment
Treat infections first with 2 - 4 drugs
Reduce number of drugs over time

Selection
Global Patterns 1994 - 1997
Drug resistance (ISONIAZID, RIFAMPIN, STREPTOMYCIN, ETHAMBUTOL)
No prior treatment
9.9% of isolates resistant to at least 1 drug
1.4% of isolates resistant to 2 or more drug
Prior treatment
36% of isolates resistant to at least 1 drug
13% of isolates resistant to 2 or more drug
Overall averages
12.6% of isolates resistant to at least 1 drug
2.2% of isolates resistant to 2 or more drug
PREVENTION

Worldwide status of TB control programs.

Three goals of WHO TB program
- Reduce mortality
- Reduce prevalence
- Reduce incidence

1960 - 1979 WHO policy
- Based on case-finding
- Treatment of sputum smear-positive cases
- BCG vaccination at birth

Outline of new WHO TB control program
- Improvement of cure rate
  - Target 85% in developing countries
  - Target 95% in industrialized countries

Cost-effectiveness of short-course chemotherapy
- Standard chemotherapy costs $15 per patient
- Short-course chemotherapy costs $30 - 40 per patient
  - Higher cure rates
  - More cost effective than standard chemotherapy
  - Combined ISONIAZID/RIFAMPIN tablets

Expansion of TB services
- Microscopic services
- X-ray equipment

Vaccines
- BCG (Bacille Calmette-Guérin)
  - Introduced in 1921
  - Derived from *Mycobacterium bovis* after repeated subculture
  - Intradermal injection of live bacillus
    - BCG contraindicated for AIDS patients
    - Used only in PPD-negative subjects
  - Results in loss of PPD as marker of new exposures
  - WHO sponsored vaccination programs
Meta-analysis of 12 case-controlled studies
- 50% efficacy in preventing TB infections.
- 78% efficacy in preventing disseminated TB infections.
- 64% efficacy in preventing TB meningitis
- 67% efficacy in preventing TB deaths.
Age of vaccination was not a predictor of efficacy.

Recommended uses of BCG
- Persons with continuous exposure to ISONIAZID and RIFAMPIN resistant TB
- Persons who cannot tolerate ISONIAZID
- Risk groups with TB infection rates >1% per year.

BOTTOM LINES
MDRTB strains increasing very little data available for world.

Clear need to expand TB programs

Clear need to increase cure rates.

HIV/AIDS makes it more difficult to control TB.

READING


FIGURE 2

Steps in the pathogenesis of TB.

Inhalation of bacteria

Bacteria reach lungs; enter macrophages

Bacteria reproduce in macrophages

Lesion begins to form (caseous necrosis)

Activated macrophages

Bacteria cease to grow; lesion calcifies

Immune suppression

Reactivation

Dead phagocytes, necrosis

M. tuberculosis

Phagocytes, T cells, and B cells trying to kill bacteria

Lesion liquifies

Bacteria coughed up in sputum

Spread to blood, organs

Death
FIGURE 3
FIGURE 4

Median CD4 counts x10 / l

- Pulmonary TB
- Nodal and extrapulmonary TB
- TB Meningitis
- Anergic Miliary TB

AFB in Tissue
FIGURE 5
FIGURE 6

[Bar chart showing the distribution of a certain percentage by age group across different countries and years.]
FIGURE 7

Immunization coverage with BCG at birth, 2003

Source: WHO/UNICEF estimates, 2004
FIGURE 8

BCG global annual reported coverage, 1980-2003

- Official coverage
- WHO/UNICEF estimated coverage