Tuberculosis
Pathophysiology and Transmission

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Tuberculosis Clinical Intensive Course

DISCLOSURE

The following planner/speaker has reported a relevant financial relationship with a commercial interest:

- Gilead Sciences Inc.
- Alere/Abbott
- Salus
Outline

• Historical Context of Tuberculosis (TB)
• *Mycobacterium spp.* and *M. tuberculosis*
• TB Pathophysiology
• TB Transmission
• Summary

Global TB Epidemic in 2018

• **Latent TB Infection**
  – ~1/3 of the world’s population
  – ~4% of the US population (11 million people)

• **Active TB Disease**
  – >10 million people with active TB, globally
    • 79% in sub-Saharan Africa
    • 1.2 million (~15%) in HIV-infected
    • 480,000 MDR-TB cases worldwide (among notified cases)
    • ~50,000 XDR-TB cases worldwide; reported by 105 countries
  – 70% of TB cases in US are reactivation of latent infection
    • HIV-negative – risk is 10% over lifetime
    • HIV-infected – risk is 10% per year
  – HIV co-infection is **21-34 times** greater risk of developing active TB disease

• **TB Mortality**
  – 1.5 million annual TB deaths
  – 400,000 (31%) were HIV-infected
  – Death rate has decreased 47% from 1990 level
  – **TB causes more deaths than any other infection, including HIV/AIDS**

Estimated TB Incidence rates, 2016

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Divided and dotted lines on maps represent approximate border lines for which there may not yet be full agreement.


Estimates of the case fatality ratio (CFR), (including HIV-negative and HIV-positive people), 2016


Global Trends in TB Incidence and Mortality

Global TB incidence is increasing or decreasing?

Global TB mortality is increasing or decreasing?

WHO. Global TB Report 2017

History of TB Medications

DISCOVERY VOID
Outline

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*Mycobacterium* spp.

• Family: Mycobactericaceae
• Highly aerobic bacillus
• Mycolic cell wall (“waxy”) with 5 layers:
  1. Capsule
  2. Mycolic acids
  3. Lipo-arabinogalactan (LAM)
  4. Peptidoglycan
  5. Plasma membrane
• Acid-fast Ziehl-Neelsen stain positive
• Non-TB Mycobacterium are ubiquitous in the environment with no person-to-person transmission, but can cause human disease
• *M. leprae* is an exception - can be transmitted through nasal secretions; humans and armadillos are only known reservoir
Non-TB *Mycobacterium* spp.

- Classification of Non-TB *Mycobacterium* spp.
  - Group 1 (photochromogens) – M. kansasii, M. marinum
  - Group 2 (scotochromogens) – M. gordonae, M. scrofulaceum
  - Group 3 (non-photochromogens) – MAC, M. terrae, M. ulcerans, M. xenopi, M. simine, M. malmuense, M. szulgai, M. asiaticum
  - Group 4 – Rapid Growers – M. fortuitum, M. chelonae, M. abscessus

- Non-TB *Mycobacterium* spp. by Organ
  - Pulmonary – MAC (“Lady Windemere’s Syndrome”), M. kansasii (most similar to TB), M. abscessus, M. xenopi
  - Lymph – MAC, M. scrofulaceum, M. bovis
  - Cutaneous – M. marinum, M. fortuitum, M. chelonae, M. abscessus, M. haemophilum
  - Disseminated – M. fortuitum, M. chelonae, M. abscessus, MAC, M. haemophilum

*Mycobacterium tuberculosis* complex

*M. tuberculosis* complex refers to genetically related group of *Mycobacterium* species that can cause tuberculosis disease in humans or others

Seven species of *M. tuberculosis* complex:

1. *M. tuberculosis* (humans - global)
2. *M. canetti* (humans in horn of Africa)
3. *M. africanum* (humans in West Africa)
4. *M. bovis* (cow, antelope; humans by dairy)
5. *M. microti* (vole)
6. *M. pinnipedi* (seal)
7. *M. caprae* (goat, cattle)
**Mycobacterium tuberculosis** complex

- Aerobic, non-motile, rod shaped bacilli
- Facultative intracellular pathogen
- Slow-growing (multiplies in 18-24 hrs)
- Thick lipid cell wall
- Acid-fast bacillus (AFB); requires special stains
- Remains dormant for decades (resists dehydration, oxidative stress, low pH)
- Resistant to most common antibiotics

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**Latent TB Infection**

- Asymptomatic people
- Mantoux PPD skin test (TST) or interferon-gamma release assay (IGRA)
- Risk factors for exposure:
  - High local TB prevalence
  - Close household contact
  - Institutional settings (hospitals, prisons, shelters)
  - Social contact (public transit)
  - Urbanization
  - Age
  - Low socioeconomic status
Active TB Disease

• Clinical Features:
  – Cough
  – Fever
  – Night sweats
  – Weight loss
  – Hemoptysis

• Diagnosed by symptoms, chest x-ray, sputum microscopy or culture

• Risk factors for active disease:
  – Proximity to contact case
  – HIV-infected
  – Immunosuppression
  – Diabetes
  – Smoking
  – Existing lung damage
  – Poor nutrition and/or low BMI
  – Host age, sex, genetics, bacterial factors

Wellcome Trust, 2012.

Relative risk of TB reactivation

Horsburgh CR, Jr. NEJM 2004;350:2060-7
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The Spectrum of Tuberculosis

- Clinical disease
- Active TB
  - Active infection
- Latent TB
  - Quiescent infection
- Infection eliminated in association with T-cell priming
- Infection eliminated without priming antigen-specific T cells
- Acquired immune response
- Innate immune response

Effect of HIV infection

Barry CE et al. Nature Reviews Micro 2009

Spectrum of TB Infection

- Early phase
  - Primary TB
  - Onset of clinical symptoms
- Late phase
  - Rapid reactivation
  - Cyclic disease
  - Slow reactivation
  - Active TB
  - Subclinical TB
  - Incipient TB
  - Latent TB
  - Latent TB
  - Latent TB
  - TB eliminated

*Increasing TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

Stage 1 – TB Pathogenesis

Stage II

Infiltrating Macrophage

Stage 2 – TB Pathogenesis
Stage 2 – TB Pathogenesis

Ghon’s complex

Week 0 - 1 2 - 3 4 - 5
Tuberculin reactive
Hematogenous dissemination

Stage 3 – TB Pathogenesis

Stage III
Unactivated Macrophage Partially Activated Macrophage Caseous Center Intact and Fragmented Bacilli
Lymphocyte
Stage 4 – TB Pathogenesis

- After *M. tb* has grown to high numbers, a ‘high moi’ death rate forms central caseation and liquefies
- This coincides with high TNF expression, inflammation, and tissue necrosis, and greater multiplication of TB
- *M. tb* subverts the host immune system (using the inflammatory response) to complete its life cycle, by passage into airways to induce cough
Granuloma – TB Pathogenesis

Bacterial vs. Host Stalemate

- **TB**
  - Uses granuloma formation to hide from host for survival/proliferation
  - Interferes with early TNF-mediated apoptosis
  - Prevents incorporation of ATP/proton pumps into the phagosome (no acidification of phagosome)

- **Host**
  - Alveolar macrophages induce phagocytosis of TB
  - Try to kill **TB** through CD4/CD8-mediated apoptosis
Increased Risk of TB Activation

- HIV-related impairment of CD4 lymphocyte functions (especially IFNγ)
- Anti-TNFα therapies prescribed for rheumatologic, inflammatory bowel disease, and other conditions
- Genetic susceptibilities:
  - Animal models – variation in susceptibility/resistance to TB
  - Twin studies – TB risk is higher among mono vs. dizygotic twins
  - Allelic variations in the NRAMP1 gene assoc. with TB susceptibility
  - Association of HLA-DR2 with vulnerability to TB
  - Familial clusters of disseminated TB infections – IFNγ receptor gene
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TB Transmission

- Patient with active, symptomatic TB disease has millions of TB bacilli
- The most important factor is droplet size
  - Intermediate-size droplets desiccate to form “droplet nuclei” (1-5 µm) to reach alveoli
  - Droplet nuclei can remain airborne indefinitely
  - *M. tuberculosis* is stable in droplet nuclei
- Coughing and sneezing projects TB
  - Cough releases 3,000 droplet nuclei
  - Sneeze release >10,000 droplet nuclei
- Average TB patient generates 75,000 infectious droplets/day before therapy
  - Decrease to 25 infectious droplets/day within 2 weeks of starting effective therapy

“Droplet Nuclei” Theory

Small droplets likely contain no TB

Intermediate droplets fall slowly, but evaporate into inhalable “droplet nuclei”

Large droplets fall to the ground quickly, before evaporating
TB Transmission

- The Baltimore VA Pilot Ward
- Effluent air passed through guinea pig cages
- Guinea pigs monitored by TST, sacrificed (and replaced) if TST+
- Time to infect one guinea pig was ~10d
- Infected animals usually had only a single lung “tubercle”

“most droplets atomized into air evaporate almost instantly, leaving disease germs drifting like cigarette smoke in the droplet nuclei”

- Wells 1948

TB Transmission

- **U.S.S. Richard E. Byrd** - 437 ft. destroyer, commissioned at Puget Sound Naval Shipyard in 1964
- Index patient: coughing with cavitary AFB smear-positive pulmonary TB
- Extensive characterization of all sailors, incl. work/sleep locations, ventilation patterns, etc.
- Overall, 139 of 308 (45%) enlisted crew converted TST; and 7 had active disease at the initial screening
- TST conversion rate was 80% in shared compartment, 53% in adjacent compartment with partially shared ventilation, and far lower elsewhere on ship

Houk et al. 1968
**TB Transmission - Droplets**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Particles ≤ 100 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing</td>
<td>?</td>
</tr>
<tr>
<td>Speaking</td>
<td>0 – 210</td>
</tr>
<tr>
<td>Speaking for 5 min</td>
<td>0 – 3,000</td>
</tr>
<tr>
<td>Coughing</td>
<td>0 – 3,500</td>
</tr>
<tr>
<td>Sneezing</td>
<td>4,500 – 1,000,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size</th>
<th>Time in Air</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 µM (“droplet nuclei”)</td>
<td>indefinite</td>
</tr>
<tr>
<td>10 µM</td>
<td>17 minutes</td>
</tr>
<tr>
<td>20 µM</td>
<td>4 minutes</td>
</tr>
<tr>
<td>100 µM</td>
<td>10 seconds</td>
</tr>
</tbody>
</table>

*Duguid 1946; Knight, NY Academy Sci, 1980*

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**TB Transmission – Risk Factors**

**CASE**

- Site of TB
- Cough
- Bacillary load
  - smear+
  - cavity
- Treatment

**CONTACT**

- Filtration
- Ventilation
- U.V. light
- Procedures
  - sputum induction
  - bronchoscopy
  - wound irrigation
  - autopsy
- Exposure/duration of contact
- Prior TB infection
- HIV
- Immunosuppressed
- Diabetes
- Smoking

*Duguid 1946; Knight, NY Academy Sci, 1980*
US Groups at Highest Risk for TB

- Close contact of TB case
- Foreign-born persons from high prevalence area
- Residents of long term care facilities
- Homeless
- Injection drug users
- Elderly persons
- Persons with occupational TB exposures

TB Transmission - Summary

- TB is spread person-to person via aerosolized “droplet nuclei”
  - Spread by persons with active TB symptoms (cough)
  - Especially cavitary, smear positive cases
  - Droplet nuclei are inhaled by the target host
- Transmission is aided by crowding, absence of UV light, and poor ventilation
- Risk depends on concentration of droplet nuclei
  - Source case factors: Rate of cough production, TB diseases
  - Environmental factors: Filtration, Ventilation, UV light
  - Contact person factors: Duration of exposure, Host resistance
TB Transmission - Airline Travel

- Limited evidence for airline transmission
- Most airlines use air filters at 3μM, which are small enough to remove droplet nuclei
- Most airplanes have 15 air-exchanges/hour
- Est. prevalence of active TB cases:
  - 0.05/100,000 (range 0 - 0.36/100,000), assuming flights to/from Africa or India

Byrne, Travel Med Infect Dis, 2007; Abubakar, Lancet ID, 2010
Clinical steps for TB suspect

• Place patient in negative pressure isolation
• Collect 3 sputum samples for AFB microscopy and culture to rule out infectious active TB
  • Spontaneous sputum expectoration (morning preferred, can do Q8H)
  • If non-productive - sputum induction with hypertonic saline
  • If still unable to get sputum - bronchoscopy with BAL
• Consider consult to Infectious Disease team
• If positive, notify TB Dept. at King County

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• The global burden of TB is severe
  – TB causes more deaths than any other infection
• Global TB incidence/deaths is decreasing
  – But, not fast enough
• Pathogenesis of TB is complicated
• Transmission remains a major problem

**Spectrum of TB Infection**

*Fig. 1: Spectrum of TB Infection.*

- **Early phase:** Primary TB, Latent TB
- **Late phase:** Cyclic disease, Infections eliminated, Reactivation, Active TB, Subclinical TB, Incipient TB, Latent TB

*Note: The spectrum illustrates the progression of TB infection and disease, with the diagram showing a timeline and pathways of infection progression. The text notes the importance of controlling this disease, given its impact on global health.*

Thank You!

Remember, World TB Day is March 24!

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