Mayo Clinic Center for Tuberculosis

TB Transmission and Pathogenesis

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Disclosures

• None
Transmission of Tuberculosis and Progression from Latent Infection to Reactivated Disease

Skin-test conversion in 6 to 8 weeks → Spontaneous healing in 6 months → Latent Tuberculosis

Progression after 2 years, 5%

Latent Tuberculosis → "Reactivation" Tuberculosis

Progression within 2 years, 5%

"Reactivation" Tuberculosis

Progression with concurrent HIV infection, 10% each year

Transmission is defined as the spread of an organism, such as *M. tuberculosis*, from one person to another.

- Centers for Disease Control and Prevention
- Division of Tuberculosis Elimination 2010
TB Transmission (3)

- TB is spread person to person through the air via droplet nuclei

- *M. tuberculosis* may be expelled when an infectious person:
  - Coughs
  - Sneezes
  - Speaks
  - Sings

- Transmission occurs when another person inhales droplet nuclei
Dots in air represent droplet nuclei containing *M. tuberculosis*
• *M. tuberculosis* causes most TB cases in U.S.

• Mycobacteria that also cause TB:
  - *M. bovis*
  - *M. africanum*
  - *M. microti*
  - *M. canetti*

• Mycobacteria that do not cause TB (not airborne)
  - e.g., *M. avium complex*
  - *M. kansasii*
# LTBI vs. TB Disease

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TB Transmission (5)

• Probability that TB will be transmitted depends on:
  • Infectiousness of person with TB disease
  • Environment in which exposure occurred
  • Length of exposure
  • Virulence (strength) of the tubercle bacilli

• The best way to stop transmission is to:
  • Isolate infectious persons
  • Provide effective treatment to infectious persons as soon as possible
Major Migration Flows: 1990s

4 x increase in volume as compared to 1960-75

Source: Population Action International 1994
Figure 1: Cabin Air Flow Patterns

Cabin Compartment
TB is spread from person to person through the air via droplet nuclei containing *M. tuberculosis*.
The probability that TB will be transmitted depends on what four factors? (pg. 11)

- Infectiousness of person with TB disease
- Environment in which exposure occurred
- Length of exposure
- Virulence (strength) of tubercle bacilli
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TB Pathogenesis
Pathogenesis is defined as how an infection or disease develops in the body.
TB Pathogenesis (2)

Latent TB Infection (LTBI)

• Occurs when tubercle bacilli are in the body, but the immune system is keeping them under control

• Detected by the Mantoux tuberculin skin test (TST) or by interferon-gamma release assays (IGRAs):
  • QuantiFERON®-TB Gold In-Tube (QFT-GIT)
  • T-Spot®. TB test (T-SPOT)

• People with LTBI are NOT infectious
TB Pathogenesis (3)
TB Disease

- Develops when immune system cannot keep tubercle bacilli under control
  - May develop very soon after infection or many years after infection
- About 10% of all people with normal immune systems who have LTBI will develop TB disease at some point in their lives
- People with TB disease are often infectious
Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli)
TB Pathogenesis (5)

2

Tubercle bacilli multiply in alveoli, where infection begins

Module 1 – Transmission and Pathogenesis of Tuberculosis
A small number of tubercle bacilli enter bloodstream and spread throughout body.
Within 2 to 8 weeks the immune system produces special immune cells called macrophages that surround the tubercle bacilli.

These cells form a barrier shell that keeps the bacilli contained and under control (LTBI).
TB Pathogenesis (8)

TB Disease

- If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease
- This process can occur in different places in the body

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*Module 1 – Transmission and Pathogenesis of Tuberculosis*
Mycobacterial Burden

- Incubating: $10^3-4$
- Latent: $10^4-5$
- TB scar: $10^6$
- Active: $10^9-11$
TB Transmission (4)

Module 1 – Transmission and Pathogenesis of Tuberculosis

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When a person inhales air that contains droplet nuclei containing *M. tuberculosis*, where do the droplet nuclei go? *(pg. 15)*

- Most of the larger droplet nuclei become lodged in the upper respiratory tract, where infection is unlikely to develop.
- However, droplet nuclei may reach the small air sacs of the lung (the alveoli), where infection begins.
After the tubercle bacilli reach the small air sacs of the lung (the alveoli), what happens to them? (pg. 15)

- Tubercle bacilli multiply in alveoli and some enter the bloodstream and spread throughout the body

- Bacilli may reach any part of the body

- Within 2 to 8 weeks, the immune system usually intervenes, halting multiplication and preventing further spread
In people with LTBI (but not TB disease), how does the immune system keep the tubercle bacilli under control? (pg. 15)

The immune system produces special immune cells that surround the tubercle bacilli. These cells form a shell (granuloma) that keeps the bacilli contained and under control.
How is LTBI detected? (pg. 16)

LTBI is detected by the Mantoux tuberculin skin test (TST) or interferon-gamma release assays (IGRA), which include the QuantiFERON®-TB Gold In-tube (QFT-GIT), or T-SPOT.
What are the major similarities and differences between LTBI and TB disease? List characteristics of each. (pg. 16)

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What happens if the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly? (pg. 16)

When this happens, TB disease develops. The risk that TB disease will develop is higher for some people than for others.
TB Pathogenesis

Progression from LTBI to TB Disease
Progression to TB Disease (1)

• Risk of developing TB disease is highest the first 2 years after infection

• People with LTBI can be given treatment to prevent them from developing TB disease

• Detecting TB infection early and providing treatment helps prevent new cases of TB disease
Conditions with increased probability of LTBI progression to TB disease

- HIV
- Substance abuse
- Chest X-ray findings of previous TB
- Recent TB infection
- Prolonged corticosteroid therapy >30 days
- TNF inhibitors

- Organ transplant
- Silicosis
- Diabetes mellitus
- Severe kidney disease
- Certain types of cancer
- Certain types of intestinal disease
- Low body weight
Progression to TB Disease (3)

People Exposed to TB

- **Not TB Infected**
  - Not Infectious
    - Negative TST or QFT-G test result
      - No TB Infection

- **Latent TB Infection (LTBI)**
  - Not Infectious
    - Positive TST or QFT-G test result
      - Latent TB Infection

May go on to develop TB disease

Figure 1.5
Progression to TB Disease (4)

TB and HIV

In an HIV-infected person, TB can develop in one of two ways:

• Person with LTBI becomes infected with HIV and then develops TB disease as the immune system is weakened

• Or:

• Person with HIV infection becomes infected with *M. tuberculosis* and then rapidly develops TB disease

Image credit: Mississippi State Department of Health
People who are infected with both *M. tuberculosis* and HIV are much more likely to develop TB disease.

<table>
<thead>
<tr>
<th>TB infection and NO risk factors</th>
<th>TB infection and HIV infection (pre-Highly Active Antiretroviral Treatment [HAART])</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram" /></td>
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</tr>
<tr>
<td>Risk is about 5% in the first 2 years after infection and about 10% over a lifetime</td>
<td>Risk is about 7% to 10% PER YEAR, a very high risk over a lifetime</td>
</tr>
</tbody>
</table>
Progression to TB Disease
Study Question 1.13

What percentage of people with LTBI (but not HIV infection) usually develop TB disease? (pg. 22)

• About 10% of all people with LTBI will develop disease at some point
  • In U.S., about 5% of recently infected will develop TB disease in first year or two after infection
  • Additional 5% will develop disease later in life
• Remaining 90% will stay infected, but free of disease, for the rest of their lives
Progression to TB Disease Study Question 1.14

What conditions appear to increase the risk that LTBI will progress to TB disease? (pg. 22)

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<td>• Organ transplant</td>
</tr>
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<td>• Chest x-ray findings suggestive of previous TB</td>
<td>• Silicosis</td>
</tr>
<tr>
<td>• Substance abuse</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Recent TB infection</td>
<td>• Severe kidney disease</td>
</tr>
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<td>• Prolonged therapy with corticosteroids and other immunosuppressive therapy, such as prednisone and tumor necrosis factor-alpha [TNF-α] antagonists</td>
<td>• Certain types of cancer</td>
</tr>
<tr>
<td></td>
<td>• Certain intestinal conditions</td>
</tr>
<tr>
<td></td>
<td>• Low body weight</td>
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Progression to TB Disease
Study Question 1.15

How does being infected with both *M. tuberculosis* and HIV affect the risk for TB disease? (pg. 22)

- Much more likely to develop TB disease
- Risk of developing TB disease is 7% to 10% EACH YEAR (pre-HAART)
- In an HIV-infected person, TB disease develops when:
  1. Person with LTBI becomes infected with HIV and then develops TB disease as the immune system is weakened
  2. Person with HIV infection becomes infected with *M. tuberculosis* and then rapidly develops TB disease
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TB Pathogenesis

Sites of TB Disease
Bacilli may reach any part of the body, but common sites include:

- Brain
- Lymph node
- Pleura
- Lung
- Spine
- Kidney
- Bone
- Larynx
## Sites of TB Disease (2)

<table>
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<tr>
<th>Location</th>
<th>Frequency</th>
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<tr>
<td><strong>Pulmonary TB</strong></td>
<td>Most TB cases are pulmonary</td>
</tr>
<tr>
<td>Lungs</td>
<td></td>
</tr>
<tr>
<td><strong>Extrapulmonary TB</strong></td>
<td>Found more often in:</td>
</tr>
<tr>
<td>Places other than lungs such as:</td>
<td></td>
</tr>
<tr>
<td>• Larynx</td>
<td>• HIV-infected or other immunosuppressed persons</td>
</tr>
<tr>
<td>• Lymph nodes</td>
<td></td>
</tr>
<tr>
<td>• Pleura</td>
<td>• Young children</td>
</tr>
<tr>
<td>• Brain</td>
<td></td>
</tr>
<tr>
<td>• Kidneys</td>
<td></td>
</tr>
<tr>
<td>• Bones and joints</td>
<td></td>
</tr>
<tr>
<td><strong>Miliary TB</strong></td>
<td>Rare</td>
</tr>
<tr>
<td>Carried to all parts of body, through bloodstream</td>
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Sites for TB
Study Question 1.16

What part of the body is the most common site for TB disease? (pg. 27)

Lungs are the most common site

What are some other sites?

- Larynx
- Lymph nodes
- Pleura (membrane around the lungs)
- Brain
- Kidneys
- Bones and joints
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Case Studies
Module 1: Case Study 1.1 (1)

A 30-year-old man visits the health department for a TST because he is required to have one before starting his new job as a health care worker. He has an 18mm positive reaction to the TST. He has no symptoms of TB, and his chest x-ray findings are normal. (pg. 16)
Module 1: Case Study 1.1 (2)

Should this be considered a case of TB?

No. The man described above has TB infection. He has an 18mm positive reaction to TST, but no evidence of TB disease. Therefore, this is not a case of TB.

Should this man be considered infectious?

No, he should not be considered infectious. This man has LTBI, not TB disease. People with TB infection and no evidence of TB disease are not infectious.
A 45-year-old woman is referred to the health department by her private physician because she was found to have LTBI as part of an employee testing program. She is obese, with high blood pressure. Upon further questioning, she reports that she has injected illegal drugs in the past, but has never been tested for HIV infection. (pg. 23)
Module 1: Case Study 1.2 (2)

What conditions does this woman have that increase the risk that she will develop TB disease?

Injection of illegal drugs increases the risk that LTBI will progress to TB disease. This woman may also be at risk for HIV infection, which is the strongest known risk factor for developing TB disease. This woman should be offered HIV counseling, testing, and referral.

Obesity and high blood pressure are NOT risk factors for TB disease.

Module 1 – Transmission and Pathogenesis of Tuberculosis