Epidemiology and Pathogenesis of TB

Sarah Buss, PhD, D(ABMM)
Wyoming Public Health Laboratory Director
Disclosures

- Nothing to Disclose
Learning Objectives

• Describe the global burden of tuberculosis (TB) and understand TB epidemiology within the US

• Explain how *M. tuberculosis* (Mtb) is transmitted and define risk factors associated with infection

• Describe the pathogenesis of Mtb
Tuberculosis in History

• Tuberculosis is one of the oldest known infectious diseases

• Mtb was identified in over 4,000 year old bone

• Assyrian tablets from 7th century B.C. describe patients with hemoptysis

• In 5th century B.C. Hippocrates wrote of patients with consumption

• TB epidemics occurred in Europe from 16th to 19th century A.D.

Tuberculosis in History

• Until mid-1800s, many believed TB was hereditary

• 1865 Jean Antoine-Villemin proved that TB was contagious

• 1882 Robert Koch discovered that Mtb causes TB
Invictus

Out of the night that covers me,
Black as the Pit from pole to pole,
I thank whatever gods may be
For my unconquerable soul.

In the fell clutch of circumstance
I have not winced nor cried aloud.
Under the bludgeonings of chance
My head is bloody, but unbowed.

Beyond this place of wrath and tears
Looms but the Horror of the shade,
And yet the menace of the years
Finds, and shall find, me unafraid.

It matters not how strait the gate,
How charged with punishments the scroll.
I am the master of my fate:
I am the captain of my soul.

William Ernest Henley
Tuberculosis in History

• TB rates dropped during the 20th century due to public health interventions, including BCG vaccine and antibiotic usage

• The decline in TB morbidity and mortality ended in the 1980s, but was reestablished in 1993
Tuberculosis Today

Estimated TB incidence rates, 2013

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MDR Tuberculosis Today

Percentage of new TB cases with MDR-TB

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MDR Tuberculosis Today

Percentage of previously treated TB cases with MDR-TB

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Tuberculosis in the US

Reported TB Cases
United States, 1982–2013*

No. of Cases

Year


*Updated as of June 11, 2014.
Tuberculosis in the US

TB Case Rates, United States, 2013

- California, Nevada, Arizona, Texas, New York, New Jersey, and Washington have rates >3.0.
- The national average is ≤3.0 cases per 100,000 population.

(CDC logo)
Tuberculosis in the US

Percentage of TB Cases Among Foreign-born Persons, United States*

2003

2013

*Updated as of June 11, 2014.

CDC

Mayo Clinic Center for Tuberculosis
MDR Tuberculosis in the US

Primary Anti-TB Drug Resistance, United States, 1993 – 2013*

% Resistant

10

5

0


Isoniazid  MDR-TB

*Updated as of June 11, 2014.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.
XDR Tuberculosis in the US

XDR TB Case Count Defined on Initial DST* by Year, 1993 – 2013**

* Drug susceptibility test.
** Updated as of June 11, 2014.
Note: Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.

Mayo Clinic Center for Tuberculosis
Tuberculosis in Wyoming
Mycobacterium tuberculosis

- Slow growing, aerobic, rod shaped bacillus
- Waxy cell wall with high lipid concentration
  - Peptidoglycan, mycolic acids, cord factor & wax-D
  - Gram-positive (but variable) & **acid fast**
- Resistant to some disinfectants & immune defenses
Transmission of Mtb

- Spread person to person via airborne droplet nuclei (1-5 µm)
- Droplet nuclei are expelled when and infectious individual:
  - Sneezes
  - Coughs
  - Sings
  - Speaks
- Transmission occurs when another person inhales droplet nuclei
Transmission of Mtb

• Probability of TB transmission depends on:
  • Susceptibility of exposed individual
  • Infectiousness of person with active TB (# of bacilli shed)
  • 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: Airborne precautions for pulmonary Tb, add Contact precautions if draining lesion
  • Provide effective treatment ASAP
TB Associated Risk Factors

Factors Associated with Increased Exposure Risk:

• Living in or travel to:
  • Sub-Saharan Africa
  • India
  • China
  • Russia
  • Pakistan

• Close contact with large populations of people
  • schools, nursing homes, dormitories, prisons, etc.

• Healthcare work or contacts of infected individuals
Pathogenesis of TB

- After inhalation droplet nuclei may be:
  - deposited on the mucous membranes and expelled, resulting in clearance and no infection
  - nonspecifically taken up by alveolar macrophages, where the infection is established and bacilli may multiply
Pathogenesis of TB

- 7-12 Days after infection, bacilli multiply within the alveolar macrophages which remain inactivated
- Lymphocytic (T cell) infiltration with accompanying cytokine release occurs leading to macrophage activation
  - **Tuberculin Skin Test** +
  - **Interferon-γ release assay** +
- Tubercle formation begins with tubercle serving as a semi-solid mass of immune cells that enable bacilli to persist, not grow
Pathogenesis of Latent TB

• Bacilli persist within tubercle, but the immune system keeps the bacilli under control

Immune cells form a barrier shell that keeps the bacilli contained and under control, resulting in noninfectious, latent TB infection (LTBI)

*A robust cell mediated immune response is triggered by the organism and results in a LTBI
Pathogenesis of Active TB

- The immune system cannot keep the bacilli in control so they escape the tubercle and rapidly multiply in the airway.

- It is estimated that an infected individual has about a 5-10% lifetime risk of progressing to active infection without treatment.
• Mφ phagocytize bacilli

• Lymphocytes are recruited to the infected, but inactivated Mφ

• Tubercle (granuloma) forms
  • Immune System keeps the infection contained, resulting in non-infectious LTBI

• Immune System fails to contain infection and granuloma spills bacilli into the airways, resulting in active pulmonary TB

• Infectious patient spews bacilli

Disseminated TB Pathogenesis

- Tubercle bacilli may spread through the lymphatic system or enter the bloodstream and travel throughout the body. This leads to extra-pulmonary TB:
  - TB lymphadenitis, pleural, skeletal, abdominal or CNS TB
  - Miliary TB: progressive and disseminated
Summary of Pathogenesis

- Inhalation of *M. tuberculosis*
  - Immediate killing of MTB (PPD-)
  - Primary complex (PPD+)
    - Stabilization (latency)
    - Localized disease (primary TB)
      - Stabilization (latency)
      - Dissemination of MTB
        - Acute disease (meningitis, miliary TB)
          - Reactivation (post-primary TB)
The Organism Pays a Role!

MTB is a fascinating organism that uses a multitude of clever mechanisms to persist within our species

- MTB inhibits normal Mφ maturation to resist killing
- MTB secretes effectors that modulate the host immune response

# Latent vs. Active Disease

<table>
<thead>
<tr>
<th>Latent TB Infection (LTBI)</th>
<th>TB Disease (in the lungs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactive</strong>, contained tubercle bacilli in the body</td>
<td><strong>Active</strong>, multiplying tubercle bacilli in the body</td>
</tr>
<tr>
<td>TST or blood test results usually positive</td>
<td>TST or blood test results usually positive</td>
</tr>
<tr>
<td>Chest x-ray usually <strong>normal</strong></td>
<td>Chest x-ray usually <strong>abnormal</strong></td>
</tr>
<tr>
<td>Sputum smears and cultures <strong>negative</strong></td>
<td>Sputum smears and cultures may be <strong>positive</strong></td>
</tr>
<tr>
<td><strong>No symptoms</strong></td>
<td><strong>Symptoms</strong> such as cough, fever, weight loss</td>
</tr>
<tr>
<td><strong>Not infectious</strong></td>
<td><strong>Often infectious</strong> before treatment</td>
</tr>
<tr>
<td><strong>Not a case</strong> of TB</td>
<td><strong>A case</strong> of TB</td>
</tr>
</tbody>
</table>
TB Associated Risk Factors

Factors Associated with Progression to Active Disease

- HIV infection or otherwise weakened immune system
- Extremes of age: babies, young children and the elderly
- Substance abuse: IV drug use, alcoholism, smoking
- Poor nutrition
- Recent infection (<2 years)
- People who were not treated correctly for TB in the past
When to Suspect TB

- Unexplained weight loss
- Loss of appetite
- Night sweats
- Fever
- Fatigue
- Coughing for longer than 3 weeks
- Hemoptysis (coughing up blood)
- Chest pain
Thank you!

sarah.buss@wyo.gov