Learning Objectives:

- Tuberculosis Terms: LTBI vs. TB Disease
- Pathogenesis of Tuberculosis
- Transmission of Tuberculosis
- Protecting Ourselves and the Public
  - TB and infection prevention tools
  - How do we determine infectivity?
  - Discharging patients safely from the hospital
  - Contact investigations: finding transmission that has already happened
- TB Diagnostic Tests (in brief)

TB: Some Important Terms

- *Mycobacterium tuberculosis* (MTB)
- Latent TB Infection (LTBI)
- TB Disease (Active Tuberculosis)
  - Primary and reactivation tuberculosis
  - Pulmonary, extrapulmonary and disseminated (miliary) tuberculosis
- Tuberculin skin test (TST) and interferon gamma release assays (IGRAs)
- AFB smears, AFB cultures and Direct Nucleic Acid Amplification (NAA) Tests

American Experience: PBS
http://video.pbs.org/video/2365422268/

Case 1

- A 41 year old Indian born male, in the US for 12 years, is admitted to a local hospital with a two day history cough with blood (hemoptysis)
- He has been generally well but does report an unintentional 10 lb. weight loss in the past 6 months
- Chest X-ray shows a right upper lobe lesion with cavity
- He is hospitalized and placed in airborne isolation, and sputum specimens are collected for AFB stain and culture

Which of the following is most important in determining his risk of having transmitted tuberculosis infection to his household contacts?

A. Level of sputum smear positivity
B. Duration and frequency of cough
C. Whether his contacts have previously been infected with Tuberculosis
D. How much time he spends in the house with them
E. All of the above are potentially important
TB Transmission

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

Transmission of Tuberculosis

- Humans are primary reservoirs.
- Person to person, airborne transmission to susceptible individuals occurs via tiny *droplet nuclei* (1-10 µm particles) allows transmission over relatively long distances (vs droplets) MTB is resistant to desiccation.
- Transmission predominantly occurs when bacteria are aerosolized by coughing or sneezing but also potentially via singing or talking (laryngeal TB).

Dots in air represent droplet nuclei containing *M. tuberculosis*.


Transmission of Tuberculosis

- Aerosolized respiratory secretions can be highly infectious, but sputum itself is not as infectious.
  - 30-45% of smear positive patients transmit TB (not all!).
  - Up to 15% of smear negative patients transmit TB.
  - Smear positivity is only one risk factor for transmission.
- Transmission generally does not occur from organisms on environmental surfaces.

Aerosolized respiratory secretions can be highly infectious, but sputum itself is not as infectious.

What Determines Risk of Transmission?

- Not all patients with pulmonary TB disease are equally likely to transmit infection to others.
- Transmission affected by:
  - Patient infectiousness: # of organisms and how effectively they are aerosolized.
  - Some correlates: smear positive, presence of cavities on CXR, cough, not being on appropriate treatment.
  - Environmental conditions (ventilation, size of room or space, etc.)
  - Duration of exposure.
  - “Virulence” of TB strain.

What Increases the Infectiousness of a Person with Pulmonary Tuberculosis?

- Coughing.
- Failing to cover their cough.
- Undergoing cough-inducing or aerosol-generating procedure (sputum induction, bronchoscopy, etc.)
- Having cavitation on chest radiograph.
- Positive acid-fast bacilli (AFB) sputum smear: being smear negative if untreated patient correlates with lower (but not zero risk).
- Inadequate TB treatment.
- Other: men> women, young adult> older, children.
Transmission Risks and Environmental Factors

- “Superspreading” environments
- Some examples of important congregate settings
  - Healthcare facilities: hospitals, offices
  - Prisons and jails
  - Bars
  - Airplanes and ships
  - Choirs
- Size, shape, ventilation
- Crowding, proximity to others
- Duration of exposure

Case 1

- His sputum smears are reported by the hospital lab as being 3+ AFB smear positive
- He was started on presumptive treatment for TB disease with a 4 drug anti-TB regimen (RIPE)
- He lives with his Indian-born wife who has history of known positive TST, two US born children, ages 18 months and 7 years, and his parents, both Indian-born, one of whom is being treated for rheumatoid arthritis with Infliximab

Who is most likely to have been infected with Tuberculosis by our presumptive* “index case” with active Tuberculosis?

A) His wife
B) His 18 month old daughter
C) His 7 year old daughter
D) His mother
E) Both of his children

*presumptive because have not yet confirmed that this is TB disease

TB Pathogenesis

Pathogenesis is defined as how an infection or disease develops in the body

TB Pathogenesis

Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli)

Source: CDC Tuberculosis Self Study Module 1 - Transmission and Pathogenesis of Tuberculosis. Available at http://www.cdc.gov/tb/education/ssmodules/

TB Pathogenesis

Tubercle bacilli multiply in alveoli, where infection begins

Source: CDC Tuberculosis Self Study Module 1 - Transmission and Pathogenesis of Tuberculosis. Available at http://www.cdc.gov/tb/education/ssmodules/
TB Pathogenesis

- 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).

Source: CDC Tuberculosis Self Study Module 1 - Transmission and Pathogenesis of Tuberculosis. Available at http://www.cdc.gov/tb/education/ssmodules/

TB Pathogenesis

- 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.

Natural History of TB Infection and Risk for TB Disease

- **TB Infection** occurs when tubercle bacilli are inhaled and settle deep in the lung of individuals who lack specific anti-TB directed immune responses (TB naïve).
- Organisms replicate and can disseminate locally in the lung and chest lymph nodes, or systemically throughout the body.
- As specific immune responses evolve, primary infection is eventually controlled in most individuals.
- A positive TST or positive IGRA is a marker of immune response to and thus infection with MTB.

Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of TB disease.

*Estimated # of individuals with LTBI in the US: 11 Million (4% of population)*

LTBI: Clinical Parameters

- Positive Tuberculosis Test
  - TST (PPD) or IGRA (QuantiFERON® Gold In-Tube or TSpot TB)
- Negative chest radiograph
- No symptoms or physical findings to indicate active tuberculosis (TB disease)
- The significance of a positive TB test cannot be determined without further evaluation

Evaluation for Active TB Disease

- CXR
- History
- Physical Exam
- If indicated (CXR or Symptoms): testing to exclude active disease Sputum smears/cultures
- DO NOT TREAT SUSPECTED ACTIVE TB AS LTBI

LTBI vs. TB Disease

<table>
<thead>
<tr>
<th>Person with LTBI (Infected)</th>
<th>Person with TB Disease (Infectious)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has a small amount of TB bacteria in his/her body that are alive, but inactive</td>
<td>Has a large amount of active TB bacteria in his/her body</td>
</tr>
<tr>
<td>Cannot spread TB bacteria to others</td>
<td>May spread TB bacteria to others</td>
</tr>
<tr>
<td>Does not feel sick, but may become sick if the bacteria become active in his/her body</td>
<td>May feel sick and may have symptoms such as a cough, fever, and/or weight loss</td>
</tr>
<tr>
<td>Usually has a TB skin test or TB blood test reaction indicating TB infection</td>
<td>Usually has a TB skin test or TB blood test reaction indicating TB infection</td>
</tr>
<tr>
<td>Radiograph typically normal</td>
<td>Radiograph may be abnormal</td>
</tr>
<tr>
<td>Sputum smears and cultures are negative</td>
<td>Sputum smears and cultures may be positive</td>
</tr>
<tr>
<td>Should consider treatment for LTBI to prevent TB disease</td>
<td>Needs treatment for TB disease</td>
</tr>
<tr>
<td>Does not require respiratory isolation</td>
<td>May require respiratory isolation</td>
</tr>
<tr>
<td>Not a TB case</td>
<td>A TB case</td>
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</tbody>
</table>

Transmission of TB Infection vs Risk of Developing TB Disease

- Newly infected are at higher risk of developing TB disease compared to others with LTBI
- But: even those newly infected can be further risk stratified as to risk of developing TB disease
- Infants, young children, and immune suppressed are at highest risk of developing TB disease compared to the “average” exposed contact
- Investigations focus on both those with highest risk of having been infected and also where the consequences of new infection are highest

Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>Advanced, untreated HIV infection</td>
<td>9.5; 9.9</td>
</tr>
<tr>
<td>Close contact with a person with infectious tuberculosis</td>
<td>6.1</td>
</tr>
<tr>
<td>Old healed Tuberculosis on CXR that is untreated</td>
<td>5.2</td>
</tr>
<tr>
<td>Prednisone &gt; 15 mg/day for &gt; 2 weeks</td>
<td>2.8</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>2.4</td>
</tr>
<tr>
<td>Treatment with a TNF alpha inhibitor</td>
<td>2.0 (but wide range)</td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>1.7</td>
</tr>
<tr>
<td>Malnutrition (&gt; 10% under ideal BW)</td>
<td>1.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.5</td>
</tr>
</tbody>
</table>


Contacts with Known History of TB Infection or TB Disease

- Individuals with prior TB infection or TB disease are relatively protected against new TB infections
  - They are still evaluated as contacts with clinical history and CXR
  - If they have already been treated previously, we generally do not treat them again, with certain exceptions
  - Re-infection can occur in those with weakened immune systems, especially HIV disease
The best way to stop transmission is to:

- Isolate infectious persons
- Provide effective treatment to infectious persons as soon as possible

And also:

- Identify contacts who are at risk for becoming (infectious) cases

When Do Patients With Pulmonary TB Become Non-Infectious?

- Significantly decreased infectivity (risk of transmission) vs no infectivity
- Criteria depend on circumstances: Where are they going and who is being exposed
- Infectivity decreases on meds, even if sputum smears positive: thus negative smears are a safe but very conservative measure of infectivity
- Generally infectivity markedly decreased after 10-14 days of effective therapy

What is the best way to determine if your patient with positive AFB smears that may be going home has TB disease (active TB)?

A. TST
B. IGRA
C. See if smears get better (become less positive) after starting treatment
D. Wait for sputum culture results
E. Send sputum for Nucleic Acid Amplification test (NAAT) for Mycobacterium Tuberculosis (MTB) such as GeneXpert MTB/RIF test or other

TB Diagnostic Tools

- For diagnosis of TB disease:
  - AFB smears and cultures
  - NAATs (molecular diagnostics)
    - MTB PCR tests
    - GeneXpert MTB/RIF
  - Chest Radiograph (pulmonary TB)
- For diagnosis of TB infection- which can be either LTBI or TB Disease
  - TST (PPD)
    - Positive Criteria for contacts of a case: 5 mm
  - IGRA testing

The hospital wants to discharge your patient home “today”. Which of the following are important in determining safe discharge to home?

- A) Negative sputum smears
- B) Decreased level of sputum smear positivity
- C) Resolution of cough and sputum production
- D) Assessment of patient cooperation with health department recommendations, including DOT and home quarantine if indicated
- E) Assessment of the home environment