Tuberculosis Overview:
TB – Yesterday, Today, and Tomorrow

Michael Lauzardo, MD MSc.
Director, Southeastern National Tuberculosis Center
Chief, Division of Infectious Diseases and Global Medicine
University of Florida

“The Lord shall smite thee with a consumption and with a fever, and with an inflammation . . . and they shall pursue thee until thou perish.”

Deuteronomy 28:22
Introduction

• Airborne disease caused by the bacterium *Mycobacterium tuberculosis* (*M. tb*)
• *M. tb* complex (*M. tb, M. bovis, M. africanum, M. microti, M. canetti, M. caprae, M. pinnipedii, and M. mungi*) can cause TB disease
• Majority of TB cases caused by *M. tb*
• *M. tb* organisms also called tubercle bacilli

TB Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>GLOBAL</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected cases</td>
<td>1.7 billion (25% population)</td>
<td>10 million (4% population)</td>
</tr>
<tr>
<td>Case incidence</td>
<td></td>
<td>9,563 in 2015</td>
</tr>
<tr>
<td>Case prevalence</td>
<td>12-15 million</td>
<td>~12,000</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.4 million/year</td>
<td>~500-550/year</td>
</tr>
<tr>
<td>MDR</td>
<td>Up to 15% (DR and Ecuador)</td>
<td>~1%</td>
</tr>
</tbody>
</table>
Reported TB Cases
United States 1982-2014
Pathogenesis and Transmission

Pathogenesis
Pathogenesis

- Droplet nuclei of 5µm or less are generated by individuals with TB and these contain 1-10 bacilli
- A single bacillus can cause disease, but 5-200 are needed to cause human infection
- Once inhaled, the bacilli become lodged in distal sub-pleural foci usually in the lower lobes
Pathogenesis

• Once deposited in the alveolar space, the bacilli are ingested by non-activated alveolar macrophages
• The bacilli are either destroyed here or multiply
• The logarithmic multiplication of bacilli is followed by cell-mediated immunity in 3-4 weeks
Pathogenesis

• During the first several weeks after infection, tubercle bacilli hematogenously spread gaining access through pulmonary lymphatics
• Spread is preferential to areas of high oxygen tension
• Usually the primary focus is eradicated within weeks or months but if progression continues – progressive primary disease
Pathogenesis

• Exposure to a person with active TB results in infection in about one third of those without HIV
• Of those infected, 3-5% develop TB within one year and an additional 3-5% develop TB at some point thereafter
Transmission

• It is hard to believe that there was much doubt as to the airborne nature of TB transmission.

• It was not until classic studies by Riley in Baltimore in the late 1950s confirmed and quantified airborne transmission.

• Tuberculosis is spread by airborne droplets ("droplet nuclei")

• Less often spread by ingestion of infected food/milk or direct inoculation
Transmission

• The studies were conducted in a ward at the VA where all the effluent air was passed through a series of cages with guinea pigs.

Transmission

• Calculated that there was one infectious dose in 11,000 to 12,500 cubic feet of air
• Infectivity of patients was very heterogeneous with eight out of 130 patients accounting for almost half of all infections.
• Untreated patients with drug-susceptible TB were much more infectious.
• Drug susceptible disease is four to eight times more infectious than resistant disease.
• UV light is very effective in preventing infection.
Transmission of Tuberculosis

Factors related to transmission are going to be related to either

Characteristics of the index patient

OR

Characteristics of contacts
Index Patient Characteristics

• Extent of disease
• Duration that source case and the contact are together and this includes proximity
• Local air circulation
• Other factors that may be important but have not been substantiated include, infective burden of MTB, previous exposure and infection, virulence, and a contact’s intrinsic predisposition for infection.

Characteristics of Contacts

• The most important characteristics determining disease progression once infected are age and immune status.
• Younger children are more likely to progress to active disease and are more likely to have short latent periods followed by potentially lethal forms of the disease.
• Therefore children under five are high priority for therapy after exposure to a case.
Immune Status

• HIV’s effects are well-known with rates of progression to active disease after infection of 35-162 per 1,000 person years.

• Other forms of immune suppression are important with progression including steroid therapy with prednisone equivalent of > 15mg per day for > 4 weeks, organ transplantation anti-rejection drugs, cancer therapy, and TNF-α antagonists.

• Other medical conditions have a lesser effect on progression after exposure.

Exposure and Transmission

• In an enclosed space the volume of air, the circulation, and the exhaust rate of the air are important predictors of transmission.

• The commonly used terms of “close” and “casual” are not defined and should be avoided.

• New contact guidelines recommend using size as a way to grade exposure settings.
Likelihood of Infection

- Depends on intensity, frequency, duration of exposure
- Most persons exposed to a person with tuberculosis do not become infected
- Cavitary or smear positive patients more infectious than noncavitary or smear negative patients
- Examples include:
  - Airline passengers seated for ≥8 hours in the same or adjoining row as a person who is contagious are more likely to be infected than others.
  - One set of criteria includes a monthly hourly total for exposure to non-cavitary cases before infection occurs (120 hours total).

Tuberculosis Infection – No Disease

- Can not spread to others (not infectious!)
- Not considered a TB case
- Positive screening test
  - tuberculin skin test (TST) or an interferon gamma release assay (IGRA)
- X-ray negative
- No symptoms
- Potential for active disease
- Treatment of Latent TB Infection (LTBI) can PREVENT TB disease
Progression from Infection to Disease is Increased by . . .

- HIV infection
- X-ray evidence of old, untreated TB
- Substance abuse, injecting drug use
- Silicosis, diabetes
- Certain therapies that affect immunity
- Certain cancers
- Underweight by 10% or more
- Very young age

Disease Progression

- Progression from infection to disease caused by an inability to contain infection
- 5-10% of all HIV(-) will progress from infection to disease
- Up to 8% per year of TST(+), HIV(+) patients will progress from infection to disease
- The average patient with active TB infects 30 other individuals
TB Classification System

<table>
<thead>
<tr>
<th>Class</th>
<th>Stage of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No exposure, no infection</td>
</tr>
<tr>
<td>1</td>
<td>Exposure, no evidence of infection</td>
</tr>
<tr>
<td>2</td>
<td>TB infection, no disease</td>
</tr>
<tr>
<td>3</td>
<td>TB, clinically active</td>
</tr>
<tr>
<td>4</td>
<td>TB, not clinically active</td>
</tr>
<tr>
<td>5</td>
<td>TB suspect</td>
</tr>
</tbody>
</table>

Diagnosis of Active Tuberculosis
Diagnosis of Active TB Disease

Key: THINK TB

Signs and Symptoms of TB Disease

• Often of long duration
• General
  - Fatigue, malaise, weight loss, fever, night sweats
• Pulmonary
  - Prolonged cough, coughing up blood
• Extrapulmonary
  - Depends on site
Diagnosis of TB Disease

• Chest x-ray
  - 95% of HIV(-) cases with upper lobe infiltrates and/or cavities

Characteristics of Chest Radiographs

• 47 patients
  - 17 with AIDS and 30 without AIDS

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>PATIENTS WITH AIDS</th>
<th>PATIENTS WITHOUT AIDS</th>
<th>P VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilar and/or mediastinal adenopathy</td>
<td>10 (59%)</td>
<td>1 (3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Localized pulmonary infiltrates involving middle or lower lung fields</td>
<td>5 (29%)</td>
<td>1 (3%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Localized pulmonary infiltrates involving upper lobes</td>
<td>3 (18%)</td>
<td>29 (97%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pulmonary cavities</td>
<td>0</td>
<td>20 (67%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No pulmonary infiltrates</td>
<td>6 (35%)</td>
<td>0</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

Adopted with permission from Am Rev Respir Dis. 1985;131:393-396.
Diagnosis of TB Disease

• Up to 30% of HIV(+), active TB cases will have no infiltrates or cavities

Extra-pulmonary TB

• ~10% in HIV(-)
• HIV(+)
  - 33% with extrapulmonary alone
  - 33% with pulmonary alone
  - 33% both pulmonary and extrapulmonary (many with negative CXRs)
• Any organ has been noted to be involved
  - Pleural dx most common
  - Lymph nodes
  - GU
  - Bone (Need to prolong therapy)
  - Abdominal
  - CNS (Need to prolong therapy)
TB Diagnosis

• Smear for acid fast bacilli (AFB)
  - Rapid preliminary presumptive diagnosis

• Culture
  - 6-8 weeks by conventional
  - 1-3 weeks by liquid media
  - Need ~100 organisms/ml to get 1 colony
  - Sensitivity-Positive in 80% CDC Verified Cases
  - Specificity- 1-2% False Positive

• Susceptibility
  - Takes 1-2 weeks after positive culture
  - Molecular Techniques give more rapid results

Most of the world does not have access to these critical laboratory tests!!!

TB Diagnosis

Nucleic Acid Amplification

• Results within eight hours 99% specificity on smear (+) cases
• Up to 80% sensitivity on three samples
• $30 to $50 per test
• Approved by the FDA for smear-positive and –negative, untreated cases
• May have a rule in non-pulmonary samples
2009 NAA CDC Guidelines

“CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations.”
Molecular Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>% mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF</td>
<td>rpoB</td>
<td>&gt;96%</td>
</tr>
<tr>
<td>INH</td>
<td>katG</td>
<td>40-60%</td>
</tr>
<tr>
<td>INH-ETH</td>
<td>inhA</td>
<td>15-43%</td>
</tr>
<tr>
<td>PZA</td>
<td>pncA</td>
<td>72-97%</td>
</tr>
<tr>
<td>F-quinolones</td>
<td>gyrA</td>
<td>75-94%</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>tlyA</td>
<td>unknown</td>
</tr>
</tbody>
</table>


GenoType MTB-DR (Hain Lifescience)
NAA Testing in Florida

• Usefulness of NAA testing in Florida:
  - Smear sensitivity around 40%, not specific for M. tuberculosis
  - At state lab, 1/2 of positive smears yields nontuberculous mycobacteria, including M. avium complex, M. kansasii, M. abcessus.
  - Rapid results may have a role in determining if the patient has or does not have TB
  - Useful for infection control, management of isolation, contact investigation decision.

NAA Testing

• Culture must be done as an adjunct
  - This is quality assurance for the NAA test
  - Must have culture for subsequent susceptibility test
Treatment of Active Tuberculosis

“How the battle against TB was won . . . and almost lost.”

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944</td>
<td>Streptomycin Introduced</td>
</tr>
<tr>
<td>1946</td>
<td>Youmans recognizes SM resistance</td>
</tr>
<tr>
<td>1951</td>
<td>Need for multi-drug therapy</td>
</tr>
<tr>
<td>1952</td>
<td>PZA introduced and INH Introduced</td>
</tr>
<tr>
<td>1961</td>
<td>EMB introduced</td>
</tr>
<tr>
<td>1966</td>
<td>Rifampin introduced</td>
</tr>
</tbody>
</table>

“The Lord hath created medicines out of the earth and he that is wise will not abhor them.”

Ecclesiasticus 38:4

Waksman Noble Prize 1952
General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with innate resistance to antibiotic action

Development of Resistance
General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with innate resistance to antibiotic action
- Slow or intermittent growth of mycobacterium which permits the persistence of viable organisms despite prolonged antibiotic treatment, because only actively replicating organisms are killed by antibiotics

Treatment of Active TB Disease

- Start with 4 drugs in all patients
  - INH, RIF, PZA and EMB until sensitivities return
  - If pansensitive, D/C EMB
  - After 2 months of therapy, D/C PZA
  - Continue INH & RIF for 4 more months for total of 6 months
- Most have culture conversion by 2 months
- 6 month regimen good for HIV(-) and (+)
- Daily or TIW therapy recommended, but BIW regimen following initial daily regimen has been by many programs
  - (TIW ? RIF Monoresistance in HIV pts after daily for first 2 months)
- Monitor adherence and toxicity
- DOT preferred, Combination pills for self administered (though SA discouraged)
Determinants of Response to Therapy

- **Clinical signs**
  - Improved cough usually within two weeks
  - Fever usually within two weeks
    - However – can last four to six weeks
  - Weight gain and improved appetite

- **Decreased organisms seen on smear**
  - Usually markedly decreased within three to four weeks
    - However – can last for months

- **Decreased counts on cultures**
  - 90% convert in two months on INH/RIF/PZA

ATS/CDC/IDSA Treatment Guidelines 2016

- **Responsibility** for successful treatment is clearly assigned to the public health departments
- **Strong recommendations** for initial patient centered case management and DOT
- **Management of TB in special situations** such as HIV, extrapulmonary TB, culture-negative pulmonary TB, and TB during pregnancy and breastfeeding
- **Recommend getting sputum** cultures at two months to identify potential relapse
- **Extended treatment** for those still with positive cultures at two months and cavities on CXR
- **Treatment completion** determined by the number of doses ingested over a given period of time.
Likelihood of Infectiousness

- Probably infectious
  - Positive sputum smears with viable AFB
  - Presence or induction of coughing
  - Not treated or recently started
  - Poor clinical or bacteriologic response to prescription
- Not infectious
  - Receiving effective therapy and responding
  - Three daily negative sputums

Causes of Inadequate Response to Therapy

- Non adherence!!!!!!!!!!!!!!!!!!!!
  - DOT
  - Involuntary detention
- Increased drug resistance/incorrect sensitivities
- Malabsorption/increased metabolism
- Inability of drugs to penetrate effected tissues
Clinical Significance of Resistance

• If pansensitive > 95% chance of cure
• If resistant to INH > 90% chance of cure
• If resistant to rifampin > 70% chance of cure
• If resistant to INH and RIF ~ 50% chance of cure
• Before chemotherapy ~ 50% chance of cure

DOT therapy works!

• 95% of patients with TB will be cured by DOT
  - Decreases morbidity and mortality and cost (~ $1500/patient)
  - Decreases spread of disease
    • Average patient with TB infects 30 other individuals
  - Decreases resistance
    • MDR costs ~ $250,000 to cure with only ~ 80% success
• 5% of patients with active TB will be unable to complete therapy requiring legal interventions and facilities to cure them
  • In S.F. one non-compliant patient with MDR-TB was responsible for 40 other cases
Infection Control

• Think TB, isolate, and start meds
• Six to eight air exchanges/hour
• Negative pressure
• Doors closed
• All entering room wear N95 mask
• Keep in isolation until three negative smears, on medications and responding clinically

Southeast National TB Center Hotline
1-800-4TB-INFO