Tuberculosis

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Vietnam Lecture Series 2001
Tuberculosis

- Mycobacterium Tuberculosis (TB) = #1 Cause of Death Worldwide from a Single Infectious Agent

TB: History

• Earliest Archeological Evidence of Spinal TB is from Egyptian Mummies, 4000 BCE.

• Earliest Evidence of Pulmonary TB 1000 BCE in a 5 Year old Boy
TB: History

• Earliest Written Description 668-626 BCE:

The Patient Coughs Frequently, His sputum is Thick and Sometimes Contains Blood. His Breathing is Like a Flute, His Skin is Cold but His Feet are Hot. He Sweats Greatly and his Heart is Much Disturbed.
TB: Ancient Names

- Hindus = **Sosha** = Cough
  **Rayakshma** = Waisting

Greeks = **Phtisis** = To Waste

English Term From Latin = **Consumption**
TB: History

- TB Peak = Industrial Revolution 17\textsuperscript{th}-18\textsuperscript{th} Century
  Resulting in 25-30\% of all Adult Deaths in Europe
TB: Epidemiology

Estimates for 1990

- World Wide # Infected = 1.7 Billion
- World Wide # Deaths = 3 Million
- SE Asia # Infected = 426 Million
- SE Asia # New Cases = 2.47 Million
- SE Asia # Deaths = 900 Thousand
TB: Transmission

- Infection = Person to Person via Airborne Infectious Aerosol:
  - Coughing
  - Sneezing
  - Talking
Transmission and Pathogenesis
TB: Transmission

- Aerosolized Droplets 5 Micrometers = 1-400 Bacilli

- Estimated 5-200 Organisms Required for Infection
TB: Transmission

• Influences on Becoming Infected:
  Infected Contact
  Duration of Exposure*
  Ventilation in Infected Environment

* Suspended Airborne Particles are Infectious after Source Leaves the Room
TB: Natural History

Inhaled Particle

Dissemination

Immune System Activation

Granuloma Formation
CXR with evidence of TB infection
TB: Disease

- Estimated Only 10% of Immunocompetent People Infected With TB (PPD+) Will Develop Clinically Significant Disease

- 50% in First 2-3 years Following Exposure
- 50% in Remote Future
TB: Disease

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TB: Determinants of Disease

- Defects in Cell Mediated Immunity
  - Advanced Age
  - Malnutrition
  - Genetic Factors
  - Immunosuppressive Meds
- Co-existing Disease: Diabetes
  - Malignancy
  - HIV
  - Renal Failure
TB: Disease Pattern

- Primary Tuberculosis
- Reactivation Tuberculosis
TB: Primary

- Associated With New TB Exposure
- Symptoms in Series of 517 New Converters:
  - Fever 70% (Duration 2-10 Weeks)
  - Chest Pain 25%
  - Pleuritic Chest Pain
  - Erethema Nodulosum Lower Extremities
    (Women > Men)
TB: Primary Chest X-Ray

- Hilar Adenopathy 64% (Children > Adults)
- Hilar Changes Right > Left
- Pleural Effusion 29% (Adults > Children)
- Unilateral Infiltrate/Ipsolateral Hilar Nodes 27%
Possible primary tuberculous pneumonia
TB: Reactivation

• Accounts For 90% of Adult non HIV TB

• Reactivation = Result of a Previously Dormant Organism Implanted Years Before by a Primary Infection

• Most Common Location = Apical Post Segment of Lung
TB Reactivation: Symptoms

- Nonspecific
- Cough 78%
- Weight Loss 74%
- Fatigue 68%
- Temperature 60%
- Night Sweats 55%
- Hemoptosis 37%
TB Reactivation: Physical Exam

• Non Specific
Apical Cavitary Disease
TB: Diagnosis

- PPD
- Sputum Examination
- Chest X-Ray
- Culture
TB: PPD

- PPD = Purified Protein Derivative

- The Tuberculin Skin Test Identifies Individuals Who Have Been Infected With Mycobacterium Tuberculosis, it Does not Differentiate Between Old and New Infection
TB: PPD

- Dose of Tuberculin = 5TU
- Injection Site = Intradermally Dorsal Side of Forearm
- Inflammatory Reaction = 24-72 Hours
- Result Test in 48-72 Hours (If Positive at 6 Days = true Positive)
Testing for TB Disease and Infection
TB: PPD Resulting

• Diameter of Induration = Determinant of Disease

• Technique: Use Ball Point Pen Start 1-2 cm Away from Margin of Test When Ball Point Pen Reaches the Margin Resistance is Felt. Repeat From Opposite Side. Distance between Lines = Diameter
Reading the Tuberculin Skin Test

- Read reaction 48-72 hours after injection
- Measure only induration
- Record reaction in millimeters
<table>
<thead>
<tr>
<th>Size of Induration</th>
<th>Considered Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5mm</td>
<td>Never = + HIV+</td>
</tr>
<tr>
<td>≥ 5mm</td>
<td>HIV+ Close Contact of TB+ + Chest X-Ray</td>
</tr>
<tr>
<td>≥ 10mm</td>
<td>IV Drugs/HIV- At Risk Disease High Risk Geography</td>
</tr>
<tr>
<td>≥ 15mm</td>
<td>All Patients</td>
</tr>
</tbody>
</table>
TB Chemo prophylaxis

- Isoniazide Prophylaxis Given to Tuberculin Reactors Reduces the Risk of Active TB by 90%
TB Chemo prophylaxis

- Isoniazid 300mg Single Daily Dose 6-12 Months
- HIV+ Patients Isoniazid 300mg Daily 12 Months
- Alternative: Isoniazid 15 mg/kg Twice Weekly 6-12 Months

*All Regiments Require Patient Compliance For Efficacy*
Risk of Isoniazid

- Hepatitis = Major Toxic Effect of Isoniazid
  - < 20 Years Old = 0% Risk
  - 20-34 Years Old = 0.3% Risk
  - 35-49 Years Old = 1.2% Risk
  - 50-65 Years Old = 2.3% Risk

Risk Increased With Alcohol Consumption
Risk of Isoniazid

- Peripheral Neuropathy

- Highest Risk in Diabetes, Malnutrition, Alcoholism

- Peripheral Neuropathy Prevention Co-Administer Pyridoxine
Micobacterium Tuberculosis in Sputum
Principles of Tuberculosis Treatment

- Regimens Must Contain Multiple Drugs
- Drugs Must be Taken Regularly
- Treatment Must be Continued for Sufficient Time (Minimal Acceptable Duration of Treatment = 6 Months)
Principles of Tuberculosis Treatment

Any Regimen is Irrelevant if Drugs Do Not Enter The Patients Body. Promoting and Monitoring Adherence to The Drug Regimen Are Essential For Treatment To be Successful
Principles of Tuberculosis Treatment

The World health Organization Advocates
Directly Observed Therapy
(DOT)
Drugs in Current Use

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Streptomycin
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (Max)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5-10mg/kg/day (300mg)</td>
<td>6 Months</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10mg/kg/day (600mg)</td>
<td>6 Months</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25mg/kg/day (2.5g)</td>
<td>First 2 Months</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>25mg/kg/day</td>
<td>First 2 Months</td>
</tr>
</tbody>
</table>
TB: Treatment Option 2

Daily: Isoniazid + Rifampin + Pyrazinamide + Ethambutol
Duration: Week 1+2

2 Times/Week: Isoniazid + Rifampin + Pyrazinamide + Ethambutol
Duration: Week 2-8

2 Times/Week: Isoniazid + Rifampin
Duration: Week 8-24

*Total Duration of Therapy 24 Weeks
*Direct Observed Therapy Required For Short Course
TB: Treatment Option 3

3 Times/Week For Total 6 Months:

Isoniazid

+  

Rifampin

+  

Pyrazinamide

+  

Ethambutol

*Directly Observed Therapy Required Short Course
# Adjusted Treatment Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>2X/Week</th>
<th>3X/Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>15mg/kg Max 900mg</td>
<td>15mg/kg Max 900mg</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10mg/kg Max 600mg</td>
<td>10mg/kg Max 600mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>50-70mg/kg Max 4g</td>
<td>50-70mg/kg Max 4g</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>50mg/kg Max 2.5g</td>
<td>50mg/kg Max 2.5g</td>
</tr>
</tbody>
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Ethambutol Caution

- Ethambutol Should not Be Used if Unable to Monitor Visual Acuity, Including in Small Children
- Substitute with Streptomycin
  
  Daily Dose = 15mg/kg Max 1g/dose  
  2x/Week Dose = 25-30mg/kg Max 1.5 g/dose  
  3x/Week Dose = 25-30mg/kg Max 1.5 g/dose
Toxicities of TB Treatment

• All therapies have significant toxicity
• All drugs are associated with hepatitis and hypersensitivity reactions
• Unique toxicities
  – INH: hepatic necrosis, peripheral neuropathy
  – Rifampin: altered drug metabolism
  – Pyrazinamide: hyperuricemia
  – Ethambutol: optic neuritis
  – Streptomycin: vestibular toxicity
Evaluation Response To Treatment

• Response To Anti TB Chemotherapy is Best Evaluated Through Sputum Examination

• Recommend Sputum Evaluation Every Month

• After 2 Months of Therapy 85% of Patients = Sputum negative
Treatment Failure

- Consider Drug Resistance To Medical regimen
- Consider Poor Patient Compliance With Medical Regimen
TB and HIV

• Complex synergy between HIV and TB
• Annual risk of progression to disease is 10%
  – this is up to 100-fold higher than in HIV -
• TB is aggressive in HIV, more likely to disseminate
• TB may be AIDS-defining illness
• Treatment is the same, but often a longer course
• Interactions between HIV meds and anti-TB drugs
TB: BCG Vaccination

- Live Attenuated Vaccine Derived From M. Bovis
- WHO: Recommended For Young Children
- Vaccination = 60-80% Decrease in Disease Does Not Prevent Infection
- Effect of BCG on PPD Decreases With Time
Allocation of TB Resources

• Infection Case Finding and Treatment

• Contact Investigation and Treatment
TB: Summary

- Endemic Disease With Significant Mortality and Morbidity
- Resource Focus: Case Finding + Contact Treatment
- Treatment Requires Medication + Compliance
CASE: I

• A 56 Year Old Previously Healthy Woman Presents for Care. She is Complaining of a Productive Cough, Fever, Night Sweats

• Past Medical History = Diabetes, She is HIV Negative

• Social = She Lives With Her Husband and 16 Year old Daughter
CASE: I

- Physical Exam
- BP 130/70  HR 90  RR 18  T 38.6
Lung: Crackles in the Right Upper lung (RUL) Field
    There is Dullness to Percussion in the RUL
Heart:  Regular Rate Rhythm No Murmers
What Studies Do You Wish to Perform?
CASE: I

- What is The Differential Diagnosis
- What is The Diagnostic Plan
- What is The Treatment Plan
- What is the Public Health Responsibility