Tuberculosis for the Hospitalist
Minnesota Chapter of the American College of Physicians Scientific Meeting
November 6, 2015
Disclosures of Financial Relationships with Relevant Commercial Interests and Off-label Uses

- None
Overview

▪ When do I need to worry about active tuberculosis?

▪ What types of active tuberculosis might I see?

▪ How do I go about diagnosing active tuberculosis?

▪ What should I be testing for when I start tuberculosis therapy?

▪ How should I treat active tuberculosis?

▪ When can I discharge this patient with active tuberculosis?

▪ What is the role of TSTs/IGRAs in the inpatient setting?

▪ What should I do if a patient has untreated latent tuberculosis?
When do I need to worry about active tuberculosis?
* Risk categories are not mutually exclusive
† Alcohol abuse and/or illicit drug use
** Conditions or therapies that increase risk for progression from latent TB infection to active TB disease, not including HIV/AIDS
Summary of Minnesota Tuberculosis Data

- Tuberculosis rates have gone down (2.8/100,000)
  - 151 cases in 2013
  - 3% have HIV

- 50% Pulm, 38% Extra Pulm, 12% Both

- 39% smear positive; 77% culture positive

- Foreign born birth is the dominant risk category (81%)
  - Somalians account for the majority of cases (29%)

- Tend to be younger, tend to be refugees (50% of foreign born)

- Majority tend to occur > 5 years out (15% in first year; 51% > 5 years)

- 54% have a form of extrapulmonary tuberculosis
N = 746

**Tuberculosis Cases by Method of Case Identification, Minnesota, 2009-2013**

- TB symptoms: 81%
- Other: 19%

*“Other” includes: other immigration exam – 1.3%, and employment screening (including health care worker screening) – 1.6%
Reasons for Delayed/Missed Diagnosis of Tuberculosis

▪ Patient is diagnosed as a community acquired pneumonia and responds to a fluoroquinolone
  ▪ Note: more than one course required for FQ resistance

▪ Atypical clinical and radiographic picture

▪ Extrapulmonary disease

▪ Clinician does not consider TB as a diagnostic possibility
What types of active tuberculosis might I see?
Textbook Presentation of Tuberculosis

- **Risk factors**: immigration from high incident area, homelessness, incarceration, IVDU, known exposure to TB

- **Classic symptoms**: prolonged cough, sputum, fever, weight loss, night sweats

- Positive tuberculin skin test (TST)

- Positive QuantiFeron/T-Spot Test

- CXR with upper lobe cavitary infiltrates
Atypical Presentation of Tuberculosis

- HIV infection, chronic renal disease, diabetes, immunosuppression may alter presentation
  - CXR may be atypical
    - Lower lobe infiltrate
    - Adenopathy
    - Completely normal (6-22%)

- Negative TST or QTF/T-Spot (20-40%)

- Negative smear (up to 50%)

- Atypical symptoms
<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>38%</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6%</td>
</tr>
<tr>
<td>Bone/Joint</td>
<td>10%</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>5%</td>
</tr>
<tr>
<td>Pleural</td>
<td>17%</td>
</tr>
<tr>
<td>Genital/Urinary</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>19%</td>
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How do I go about diagnosing active tuberculosis?
How is *M. tuberculosis* Identified from Clinical Samples?

- **AFB Smear**
  - Estimated 10,000 bacilli/mL to produce a positive smear
  - AFB staining of sputum
    - Ziehl-Neelsen
    - Auramine-rhodamine

- **Pros**
  - Rapid, simple

- **Cons**
  - Poor sensitivity
  - Cannot identify the species involved
How is *M. tuberculosis* Identified from Clinical Samples?

- **Culture**
  - **Liquid** broth (Middlebrook 7H12)
    - Automated
    - Require 1-3 weeks
    - More sensitive than solid media

- **Pros**
  - Good sensitivity
  - Drug susceptibility

- **Cons**
  - Slow
  - Infrastructure
How is *M. tuberculosis* Identified from Clinical Samples?

- **Nucleic acid amplification (NAAT)**
  - Two assays available
    - Gene-Probe Direct Test (rRNA)
    - Roche AMPLICOR (DNA)

- **Pros**
  - Same day results
  - Sensitivity intermediate between acid-fast stain and culture for smear positive cases
  - 40-77% sensitivity for smear negative cases
  - Identifies organism as *M. tuberculosis* complex

- **Cons**
  - Labor intensive
How is *M. tuberculosis* Identified from Positive Cultures?

- **Nucleic acid probes**
  - Results in 2 h
  - Sensitivity/Specificity near 100%
  - Requires $10^5$ organisms (used on cultures, not clinical specimens)
  - Identifies organism as *M. tuberculosis* complex

- **Capilia TB-Neo**
  - Strip-based species identification (MTb vs not MTb) in positive cultures based on the detection of MPB64 antigen specifically secreted by MTb
  - Used on cultures, not clinical specimens
  - Accurate, minimal training
Molecular Beacon (MB) Testing

- Identification of *M. tuberculosis* complex
- Screening for INH and RIF resistance
- Employs realtime PCR
  - Short oligonucleotide probe that contains a sequence complimentary to wild-type MTb sequences of:
    - katG gene and inhA gene promotor (82% sensitive)
    - 3 MBs for the core region of the *rpoB* gene (98% sensitive)
- Performed on AFB smear positive sputum samples or positive cultures
- Limitations
  - Insufficient DNA, non-TB or inhibitory substances
  - Mixed culture (false negative)
  - Silent mutations (false positive; rare)
  - Heavy contamination (false negative)

Lin et al. J Clin Microbiol. 2004 Sep;42(9):4204-8
Xpert® MTB/RIF

- The Xpert MTB/RIF detects DNA sequences specific for MTb and rifampin resistance by PCR.
Current tuberculosis diagnostics pipeline listing the development phases and the types of technologies in development or evaluation

<table>
<thead>
<tr>
<th>High Complexity Assays</th>
<th>Moderate Complexity Assays</th>
<th>Low Complexity Assays</th>
</tr>
</thead>
</table>

**Molecular Detection/DST**
- TrueNat MDR-TB (Akkord)
- CUBAS (Cepheid MTB + IS6110/Roch)
- Hydro X (Hoffmann-La Roche)
- Mycobacterium Real-time MDR (CapitaBio)

**Late or Completed Development**
- TRIC Rapid MTB (Tricoh)
- VeniMTB (Wessex Laboratories)
- LPA Pustulonamid (Rippe)
- LATE-PCR lights on / lights off (Hain)
- TBFin (Abebio)
- Mettyp (Ozeran)
- Mycobacterium RT-PCR/CapitaBio
- RIBA MTB-XDR (VD Diagnostics)
- Enzyme Kit (Unicon)
- BD Max (BD)

**On Pathway to WHO Evaluation**
- GenoTYP MTB (Hain)
- LPA-MDR-TB (Patho)
- RIBA MTB-RIF (VD Diagnostics)

**Culture-based Technology**
- BNP MiteBacteri (NanoLogix)
- Rapid colorimetric DST

**Antigen & Antibody Detection**
- LAM in sputum (Standard Diagnostics)
- Multiple antibody array (mBla)

**Enzymatic Detection**
- β-lactamase reporter (Global BioDiagnostics)

**Source:** FIND, Geneva

Madhukar Pai, and Marco Schito J Infect Dis. 2015;211:S21-S28
How should I treat active tuberculosis?
Provider Responsibilities

- The overall goals for treatment of tuberculosis are:
  - to cure the individual patient
  - to minimize the transmission of *Mycobacterium tuberculosis* to other persons

- The prescribing physician is carrying out a public health function with responsibility not only for prescribing an appropriate regimen but also for **successful completion of therapy**

- Prescribing physician responsibility for treatment completion is a fundamental principle in tuberculosis control
# How Do We Treat Tuberculosis?

**First-Line Drugs**
- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine

**Second-Line Drugs**
- Streptomycin, Capreomycin, Amikacin or Kanamycin*
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Levofloxacin*, Moxifloxacin*, Gatifloxacin*
- Bedaquiline (2014)

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB

**MMWR 2003. 52:RR-11;1-80**
Standard Tuberculosis Treatment Regimen

- **Initial phase**: standard four drug regimens (INH, RIF, PZA, EMB), for 2 months
  - Large bacterial burden

- Goal is to rapidly reduce number of bacilli present to render non-infectious
  - Time period when resistance most likely to develop
Standard Tuberculosis Treatment Regimen

- **Continuation phase**: additional 4 months or (7 months for some patients)
  - Smaller bacterial burden
  - Goal is to treat long enough to prevent relapse
How Does Directly Observed Therapy (DOT) Work?

- Outreach workers provide medications to the patient Monday-Friday
  - Outreach workers meet patients at their home, work, school, or other locations
- Patients take their own medications on weekends and holidays
- Outreach workers are a valuable resource to assess patient’s compliance, complications, and questions
Active Tuberculosis and HIV Disease

- Start TB medications immediately
- Treatment duration extended to 9-12 months
- Initiate ART within 2 weeks with CD$_4$ < 50
- Initiate ART in 2-4 weeks with CD$_4$ >50 with severe clinical disease
- Initiate ART in 8-12 weeks with CD$_4$>50 without severe clinical disease
- Initiate ART in 2-4 weeks with MDR/XDR tuberculosis
What should I be testing for when I start tuberculosis therapy?
Patient Education

▪ Explain what tuberculosis disease is

▪ Address any cultural bias/misinformation

▪ Explain any and all public health implications

▪ Explain what DOT is
  ▪ Emphasize it’s place in standard of care
  ▪ Emphasize the customer service aspect
Initial Basic Monitoring

- Symptom review
- Weight/nutritional assessment
  - Provide supplementation if needed
- Testing for HIV infection
  - CD$_4^+$ T-lymphocyte count for HIV-positive persons
- Hepatitis B and C serologic tests, if risks present
- Baseline CXR, CBC + platelets, liver function tests, creatinine
- Visual acuity and color vision tests (when EMB used)
When can I discharge this patient with active tuberculosis?
Inpatient Pulmonary Tuberculosis Patient

- Default position is to remain inpatient until sputum samples x 3 are smear negative
  - Median time to clearance is 2 weeks

- Local Public Health Clinic/Minnesota Department of Health can help assess:
  - Home situation for potential home isolation
  - Assist in arranging transition to outpatient DOT therapy
Cumulative Diagnostic Yield of Induced Sputum

- One Sputum:
  - Smear: 64%
  - Culture: 70%

- Two Sputum:
  - Smear: 81%
  - Culture: 91%

- Three Sputum:
  - Smear: 91%
  - Culture: 99%

- Induced sputum samples are no better than spontaneous sputum samples
- BAL samples are no better than induced sputum samples

Al-Zahrani et al
What is the role of TSTs/IGRAs in the inpatient setting?
Which of the following is true of IGRAs for detecting latent tuberculosis?

- A) IGRAs can detect tuberculosis infection earlier than TSTs after a known exposure

- B) IGRAs can distinguish active from latent tuberculosis

- C) IGRAs are more specific for *M. tuberculosis* complex than TSTs

- D) IGRAs are best utilized by serial testing over a period of months
Reasons to order an IGRA in an inpatient setting

- Screening for tuberculosis infection (latent tuberculosis)
  - Anticipated immunosuppression in the near to intermediate future due to cancer chemotherapy, biologics, solid organ transplantation, or stem cell transplantation
    - A lag time of 4 weeks between INH initiation and anti-TNF starting is considered safe by most experts and the majority of the international recommendations
  - New diagnosis of HIV

- NOT USEFUL FOR RULING IN OR RULING OUT ACTIVE TUBERCULOSIS
  - IGRA negative 20-40% in active tuberculosis cases

J Rheumatol Suppl 2014;91:41–6
What should I do if a patient has untreated latent tuberculosis?
Treatment of LTBI

- INH x 9 months (90% reduction)
  - INH x 6 months (70% reduction)

- Rifampin 600mg daily x 4 months for adults
  - Rifampin daily for 6 months for children

- Rifapentine & INH weekly x 12 doses by DOT

Division of Tuberculosis Elimination
Centers for Disease Control and Prevention, 2005
Compliance

- Only 30-60% of patients who start treatment complete at least 6 months

- Adherence decreases with time while efficacy increases with time!

- Refer to public health department for management if running into difficulties