Lisa Armitige, MD, PhD has the following disclosures to make:

- No conflict of interest.

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Diagnosis and Treatment of Tuberculosis

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Pathogenesis of Tuberculosis
Outcomes of Exposure to *M. tuberculosis*

Inhalation of Droplet Nuclei

\[ \downarrow \]

Regional replication in lungs, dissemination

\[ \downarrow \sim 90\% \quad \downarrow \sim 5\% \quad \downarrow \sim 5\% \]

Killing, containment of organisms  Latent disease  Active disease

Transmission of *M. tuberculosis*
Sites of TB Disease

• Lungs

Extrapulmonary:

• Larynx
• Pleural effusion
• Kidneys
• Lymphatics
• Bones & joints
• Miliary (disseminated)

Signs & Symptoms
Pulmonary TB

Pulmonary Symptoms:

• Productive prolonged cough of over 3 weeks duration
• Chest pain
• Hemoptysis

Systemic Symptoms:

• Fever
• Chills
• Night sweats
• Appetite loss
• Weight loss
• Easy fatigability
Extrapulmonary TB

- More of a diagnostic problem than pulmonary TB
- Involves inaccessible sites = fewer bacteria can cause greater damage
- Bacteriologic confirmation more difficult
- Most forms represent reactivation TB

Diagnosing Tuberculosis
Evaluation for TB

• Medical history
• Physical examination
• Testing for TB infection
• Chest radiograph
• Bacteriologic or histologic exam

Medical History

• Prior TB exposure, infection or disease

• Past TB treatment

• Demographic factors: country of origin, age, ethnic or racial group, occupation
Medical History

- HIV Infection
- Substance abuse
- Recent exposure
- Diabetes mellitus
- Silicosis
- Prolonged Corticosteroid therapy
- Immunosuppressive therapy
- Cancer of head and neck
- Hodgkin’s lymphoma
- Leukemia
- End-stage renal disease
- Intestinal bypass
- Gastrectomy
- Chronic malabsorption syndromes
- Low body weight

*Patients suspected of TB infection or disease who do not know their HIV status should be referred for HIV counseling and testing*
Physical Exam

• Cannot be used to confirm or rule out TB

• Can provide valuable information about the client’s overall health

Testing for TB Infection

• A TST or IGRA may help differentiate infected from uninfected people with signs and symptoms

• A negative TST or IGRA does not exclude the diagnosis of TB (especially for patient’s with severe TB illness or infection with HIV)
The Tuberculin Skin Test (TST)

- 0.1 ml of 5 TU PPD tuberculin injected intradermally
- Induration in millimeters read 48-72 hours after injection

Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients
Classifying the Tuberculin Reaction

10 mm is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Classifying the Tuberculin Reaction

15 mm is classified as positive in

- Persons with no known risk factors for TB
- Targeted skin testing programs should only be conducted among high-risk groups
IFN-γ (gamma) release assays (IGRAs)

Antigens for Newer Generation IGRAs

- Negative control or nil (e.g., saline, heparin)

- Positive control or mitogen: non-specific immune response stimulator (e.g., phytohemagglutinin)

- *M. tuberculosis*-specific antigens
  - Unlike PPD used in TST, do not cross-react with BCG or NTM (some exceptions)
  - ESAT-6, CFP-10, TB 7.7 (actually simulated using overlapping peptides)
### Antigens for Gamma-Release Assays

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<th>Tuberculosis complex</th>
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CDC IGRA Recommendations

• TST or IGRAs should be used as aids in diagnosing infection with *M. tuberculosis*
  – Both the standard qualitative test interpretation and the quantitative assay measurements should be reported

• As with the TST, IGRAs generally should not be used for testing persons who have a low risk of infection and a low risk of disease due to *M. tuberculosis*

• Selection of the most suitable test or combination of tests for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and cost effectiveness of testing

CDC IGRA Recommendations

• IGRAs may be used in place of (and not in addition to) TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection, with preferences and special considerations as follow

• Despite the indication of a preference, use of the alternative test (IGRA or TST) is considered acceptable medical and public health practice
CDC IGRA Recommendations

• Populations/situations in which IGRA are preferred
  – testing persons from groups that historically have poor rates of return for TST reading
  – testing persons who have received BCG (as a vaccine or for cancer therapy)

• Populations/situations in which TST is preferred
  – testing children younger than 5 years old

• Populations/situations in which there is no preference between IGRA and TST
  – testing recent contacts of persons with infectious tuberculosis
  – periodic screening that addresses occupational exposure to TB (e.g., surveillance programs for healthcare workers)

Testing for TB Infection

• Clients who have a positive TST result, a positive IGRA result or symptoms suggestive of TB (regardless of TST results) should be evaluated with an CXR

• If abnormalities are noted, or the client has symptoms suggestive of extrapulmonary TB, additional diagnostic tests should be conducted
No CXR study shows findings specific for TB

Cavitary process are more likely to be TB

Common mimics of TB =

- Non-tuberculous mycobacteria (NTM)
- Fungal infection
- Bacterial abscesses
- Necrotic neoplasm (especially lung neoplasm)

Chest Radiograph (CXR)

- Cannot confirm diagnosis of TB disease
- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV positive persons
CXR – HIV infected persons

- May cause infiltrates without cavities in any lung zone
- May cause mediastinal or hilar lymphadenopathy with or without infiltrates or cavities

In HIV-infected persons almost any abnormality on CXR may indicate TB
Miliary Tuberculosis
CXR – old healed TB

- Dense nodules, with or without visible calcification (hilar or upper lobes)
- Smaller nodules with or without fibrotic scars (upper lobes, often with volume loss)

Old healed TB nodules & fibrotic lesions have well-demarcated sharp margins
• Nodules & fibrotic lesions may contain slowly multiplying bacilli = potential for progression

• CXR consistent with old TB and + TST/IGRA = high priority for LTBI treatment

Calcified nodular lesions (calcified granuloma) pose a very low risk for future progression
CXR - special situations

• Pregnant women who are highly suspicious and being evaluated for active disease should undergo a CXR without delay, even during the first trimester

• Patients suspected of extrapulmonary TB should have a CXR to R/O pulmonary TB

Clinical Presentation
HIV-positive vs. HIV-negative patients

• Driven mostly by degree of immunity

• HIV-positive patients are more likely to have:
  – Isolated extrapulmonary localization (53-63% in some studies)
  – Primary infection
  – Pulmonary basilar involvement
  – Tuberculous pneumonia
  – Hilar or mediastinal lymphadenopathies
  – Miliary or disseminated TB
  – Normal CXR (8-20% in some studies)
**Bacteriologic and Histologic Examinations**

When lung or larynx is site of disease:

- 3 sputum specimens for AFB smear and culture
- Collected 8-24 hours apart with at least 1 early morning specimen

**Bacteriologic and Histologic Examinations**

- Sputum collection should be directly supervised
- For patients unable to cough up sputum, deep coughing may be induced
Bacteriologic and Histologic Examinations

Bronchoscopy

• Bronchial washings
• Brushings
• Biopsy specimens

Sputum collected after bronchoscopy may also be useful for a diagnosis

Extrapulmonary Specimens

• Urine
• Cerebrospinal fluid *
• Pleural fluid *
• Pus
• Biopsy specimens

*recovery poor

Do NOT collect specimens in Formalin
Laboratory Examination

AFB Smear

- First clue
- Presumptive diagnosis only

- Fluorochrome staining preferred method
- Results available in 24 hours
- Many patients have negative AFB smears

Cultures

- Used to confirm diagnosis
- Perform on ALL specimens regardless of AFB smear results
- Results available in 10 to 14 days (on liquid media, e.g. BACTEC)

*TB may be diagnosed on the basis of signs and symptoms in the absence of a positive culture*
Laboratory Examination

- Nucleic acid probes ID species in 2 to 4 hours
- HPLC are equally rapid and can ID most species
- Solid mediums and conventional tests can take 6 to 12 weeks

Laboratory Follow-up

- Monitor sputum cultures at least monthly until negative cultures are obtained
- Culture conversion = 1st negative culture in a series of previously positive cultures (all subsequent cultures must remain negative)
Treatment of Tuberculosis

ANTITUBERCULOSIS DRUGS
(ATS/CDC/IDSA)

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

- Second-Line Drugs
  - Cycloserine
  - Ethionamide
  - Levofloxacin*
  - Moxifloxacin*
  - PAS
  - Streptomycin
  - Amikacin/Kanamycin
  - Capreomycin

*Not FDA approved for TB
ANTITUBERCULOSIS DRUGS

• INH (Isoniazid)
  – Accounts for the majority of early bactericidal activity of multi-drug TB regimens
  – Excellent absorption and tissue penetration

• Rifampin
  – Bactericidal (highest sterilizing activity).
  – Activity against rapidly dividing and against semi-dormant bacterial populations.
  – Cornerstone of short course therapy
  – Well absorbed, good tissue levels
  – Longer-acting Rifapentine being investigated

ANTITUBERCULOSIS DRUGS

• Ethambutol
  – Included in first-line treatment regimens to prevent the emergence of Rifampin resistance when INH resistance may be present.

• PZA (pyrazinamide)
  – Bacteriostatic/sterilizing agent: Greatest activity against dormant or semi-dormant (slowly growing) organisms within macrophages or caseous foci (acidic environment).
  – Necessary for 6 months treatment regimen
ANTITUBERCULOSIS DRUGS

• Fluoroquinolones
  – Preferred oral agents for treating drug resistant TB that is susceptible to this class of drugs or for patients intolerant of first-line drugs
  – Activity against MTB: Moxifloxacin > levofloxacin > ofloxacin/ciprofloxacin
  – Cross resistance

Initiating Treatment for LTBI

Before initiating treatment for LTBI
• Rule out TB disease
  – i.e. wait for culture results if specimen obtained
• Determine prior history of treatment for LTBI or TB disease
• Assess risks and benefits of treatment
• Determine current and previous drug therapy
Isoniazid Regimens for LTBI

- 9-month regimen of isoniazid (INH) is the preferred regimen

- 6-month regimen is less effective but may be used if unable to complete 9 months

- May be given daily or intermittently (twice weekly)
  - Use directly observed therapy (DOT) for intermittent regimen

Persons with the following conditions need special precautions while on isoniazid

a. Age 35 years and over
b. Taking other medications on a long term basis
c. Alcohol abusers
d. History of previous discontinuation of isoniazid because of toxicity/adverse reactions
e. Chronic liver disease
f. Peripheral neuropathy
g. Pregnancy
Rifampin Regimens for LTBI

- Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.

- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

- RIF and PZA for 2 months should generally not be offered due to risk of severe adverse events.
Updates and Changes in TB Therapy

- Obtain a sputum smear and culture at the end of the initial phase of treatment (2 months) to identify patients at increased risk of relapse.

- Extended therapy is recommended for patients with drug-susceptible pulmonary TB who have cavitation on the initial CXR and who have a positive sputum culture at the time 2 months of therapy is completed.

- Counting Doses – treatment completion is defined by number of doses taken as well as duration of treatment.

Updates and Changes in Therapy

- Changes in dosing schedules:
  - HIV + individuals with low CD4 counts should NOT be given twice weekly therapy.
  - Daily therapy can be 7 days per week OR can be 5 days per week IF given by DOT and the Mtb is drug susceptible.
Role of New Agents

• **Rifabutin (RBT):**
  – May be used as a primary drug for patients (especially HIV+) receiving medications having unacceptable interactions with rifampin (e.g. Protease Inhibitors, methadone)

• **Fluoroquinolones:**
  – May be used when first line drugs are not tolerated or the organism is resistant
  – Moxifloxin rapidly becoming agent of choice

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

• **General conclusions from the literature**
  – 6 mo (26 wk) is the MINIMUM duration of Rx
  – 6 mo regimens require rifampin throughout and PZA for the first 2 months
  – 6 mo regimens are effective without INH
  – Intermittent regimens (2-3x/wk):
    • GIVEN by DOT ONLY
    • Drug susceptible isolate
    • Regimen contains INH and rifampin
Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature:
  - Without PZA - minimum duration is 9 months
  - Without rifampin - minimum duration is 12 months (up to 18 months)
  - Streptomycin and ethambutol (EMB) are approximately equivalent in effect (BUT concern about increasing Streptomycin resistance among foreign born leads to preference of EMB for initial therapy)

Treatment of Patients with TB Disease

- Initiation phase of therapy
  - 8 weeks; INH, Rifampin and PZA +/- EMB
- Continuation phase of therapy
  - 16 weeks; INH and Rifampin
- Prolongation of continuation phase
  - Positive 2 month culture with cavitary disease
  - Extrapulmonary disease
    - Meningitis
    - Disseminated disease in children
  - HIV TB in children and adolescents
- Consider Prolongation of continuation phase when patient:
  - Slow to clinically or radiographically respond
  - Positive 2 month culture OR cavitary disease?
  - End of therapy (EOT) cavity present
  - <10% ideal body weight?
Relapsed Tuberculosis

- Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later

- Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms
  - Treat with standard RIPE regimen

Treatment Related Risk Factors for Early Relapse of TB

- Evaluation of 113 cases of relapsed TB when matched with case controls
  - Non-cavitary TB, relapse rate: 1.1%
  - Cavitary TB relapse rates:
    - Thrice weekly Rx: 7.8%
    - Daily Rx: 3.3%
    - Extended thrice weekly: 0.5%
    - Extended daily: 0.4%
    - Extending either intensive phase or both was beneficial

Chang, Am J Respir Crit Care Med. 2004; 170: 1124-30
Medical Factors Associated With Relapse of Tuberculosis

- Cavitary TB
- Extensive disease on CXR; bilateral infiltrates
- Positive 2 month culture
- Associated medical conditions
  - Diabetes
  - HIV
  - Malabsorption of TB drugs
- Tuberculous lymphadenitis
- Underweight at diagnosis and failure to gain
- Drug resistant disease
- Prior treatment for tuberculosis

Active TB During Pregnancy

- Treatment:
  - INH, Rifampin, Ethambutol x 9 months
    - Stop ethambutol if susceptible to INH and rifampin
  - PZA only if drug resistance is present
    - PZA regarded as safe by most countries in world
      (only US and Australia don’t)
- Follow carefully for hepatotoxicity
  - During pregnancy
  - Three months postpartum
Management of Treatment Interruptions

- **Initial phase of therapy**
  - <14 days – complete standard # of doses
  - >14 days – restart from the beginning

- **Continuation phase**
  - >80% doses by DOT – if initial smear negative, may stop
  - Repeat culture
    - >3 month interruption restart from beginning
    - <3 month interruption, culture positive, restart
    - <3 month interruption, culture negative, give an additional 4 months

Drug-Resistant Tuberculosis
MDR TB – Definitions
TB resistant to INH and Rifampin

• TB - No Prior Therapy
  aka
• Primary MDR TB
  – Results from exposure to a patient with infectious MDR TB

• TB – Prior Therapy
  aka
• Acquired MDR TB
  – Results from inadequate treatment and/or non adherence

XDR TB

• MDR TB
  – Plus resistance to one of the fluoroquinolones
    • Ofloxacin
    • Levofloxacin
    • Moxifloxacin
    AND
  – Resistance to one of the second line injectables
    • Amikacin
    • Capreomycin
    • Kanamycin
Why Do We Have Drug Resistance?

• Inadequate Treatment
  – Incorrect regimen (lack of drugs or knowledge)
  – Poor adherence

Which Patients are at Risk of Drug Resistant TB?

• Birth/residence in country with high incidence of drug resistant TB
• U.S. residents who travel to high risk areas
• Exposure to patient with relapse or failure

• Prior treatment for TB
• Treatment failure
• Relapse in a patient not on DOT
• Poor adherence
• Clinical deterioration during 4 drug therapy
If You Diagnose MDR/XDR TB -

• This would be a good time to consider medical consultation!

  but really

• Anytime you have a question is a great time

Principles of Treatment and Management of MDR TB

• Treat patients with likely drug resistant disease with an adequate number of drugs to prevent emergence of further resistance (amplification of resistance).

• Use 5 active drugs initially
  – Use more drugs if susceptibility tests pending
  – 5 or > drugs associated with better outcomes
Management of Contacts of MDR TB

• Treat for 6 months or observe without treatment
  • Use drugs source case is sensitive to
    • Choose 2: EMB, FQN, PZA
  • HIV positive and immunocompromised persons should be encouraged to accept treatment
    • Treat HIV-positive persons for 12 months

• Follow for 2 years regardless of treatment
  • CXR and clinical evaluation

THEY ALWAYS COME BACK

Do It Right The First Time!

Barbara Seaworth