Diagnosis and Treatment of Tuberculosis, 2011

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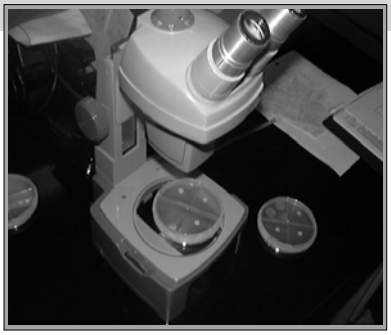
Diagnosis of TB



Diagnosis of TB, 2011

- **Diagnosis follows "*Suspicion*"**
- **When should we "*Think TB*"?**
  - Who is at risk for TB?
  - Is TB presenting differently than in the past?
  - How do we make the diagnosis?
  - And … are there new ways to improve diagnostic capacity?

Define Groups at-Risk

- **Epidemiology of recent cases**
  - **Majority of cases are non-US born from high prevalence countries**
  - **Community-specific (*e.g., homeless, substance abusers, Haitians*…)**
  - **Children from high-prevalence groups**
- **Medical risk factors *(if infected)***
  - **HIV 7-10% / yr**
  - **Diabetes 4% / yr**
  - **ESRD 10-20% / yr**
  - **Immunosuppressive therapies (e.g., *organ transplant recipients*, *anti-TNF-α agents*, *chronic steroids)***
  - **Age**
- **Recent transmission *versus* reactivation**
  - **TB still a problem among US-born elderly US-born still appear (usually represent reactivation)**

Evaluation for TB

- **Medical history**
- **Physical examination**
- **Mantoux tuberculin skin test / IGRA**
- **Chest radiograph**
- **Bacteriologic or histologic exam**

TB Symptom Assessment

Symptoms of pulmonary TB

- **Persistent cough, productive or non-productive**
- **Chest pain, hemoptysis**

  +/- Anorexia, weight loss

  +/- Fever, chills, night sweats

*** 25% of people with active pulmonary TB are asymptomatic**

***Charles Daley, MedPage Today July 27, 2007**

Medical History

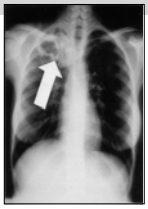
- **Symptoms of disease**
- **History of prior TB exposure, infection, or disease**
- **Past TB treatment (TB regimen, completion status)**
- **Demographic risk factors for TB**
- **Medical conditions that increase risk for TB disease**

Tuberculin Skin Test and IGRA

- **TST can be used in the diagnosis of TB disease but is less sensitive during severe illness**
- **IGRA is approved for use in both diagnosis of latent or active TB**

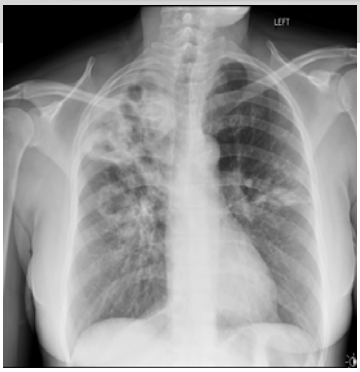
Chest Radiograph

- **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**
- **Cannot confirm diagnosis of TB**



Arrow points to cavity in patient's right upper lobe

Chest X-ray



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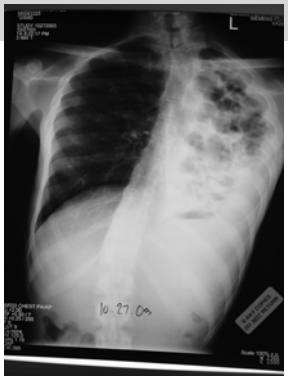

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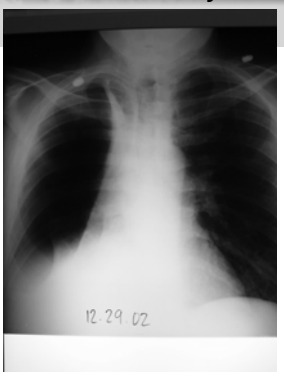


Bacteriologic Exam

- **Smear examination and culture**
  - Follow infection control precautions during specimen collection
- **TB diagnosis confirmed by culture**

Drug Susceptibility Testing

- **Drug susceptibility testing for initial *M.tb* isolate**
- **Repeat for patients who**
  - Do not respond to therapy
  - Have positive cultures despite 2 months of therapy
- **Communicate with lab for prompt reporting**

Nucleic Acid Amplification Tests

- **PCR is a more sensitive assay that can be applied directly**
- **Detection of *M. tuberculosis* in laboratory specimen**
- **Detection of mycobacteria in clinical specimen**
  - Pulmonary TB: smear positive / negative (positive predictive value = 75%)
  - Extrapulmonary TB – meningitis, pericarditis, pleurisy

Other Routine Examinations

- **Testing for HIV infection**
  - CD4+ T-lymphocyte count for HIV-positive persons
- **Hepatitis B and C serologic tests, if risks present**
- **Measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, serum creatinine, and platelet count**
- **Visual acuity and color vision tests (when EMB used)**

Treatment of Tuberculosis

Responsibility for Successful Treatment

- **Goals for treatment of TB are to cure the individual patient and to minimize transmission of *M.tb***
- **Successful treatment benefits the individual patient and the community**
- **Responsibility lies with health care provider, not only for prescribing appropriate regimen, but for ensuring successful completion of therapy**

"A decision to start TB treatment is a decision and obligation to cure the patient."

Management Strategies

- **Circumstances surrounding each patient may affect their ability to complete treatment**
- **Case management, using a patient-centered approach**
- **Interventions using enablers to assist in completion of therapy (transportation, convenient clinic hours, bilingual staff)**
- **Interventions using incentives meaningful to the patient (movie passes, gift cards, meal vouchers, clothing)**
- **Individualized care plan for completion including directly observed therapy (DOT)**

Factors Guiding Treatment Initiation

- **Epidemiologic information**
- **Clinical, pathological, chest x-ray findings**
- **Microscopic examination of acid-fast bacilli (AFB) sputum smears and cultures**
- **Rapid diagnostic tests (nucleic acid amplification test)**

Treatment Initiation

- **Positive AFB smear**
- **Treatment should not be delayed because of negative AFB smears if high clinical suspicion:**
  - History of cough and weight loss
  - Characteristic findings on chest x-ray
  - Emigration from a high-incidence country

Antituberculosis Drugs Currently in Use

First-Line Drugs

- **Isoniazid**
- **Rifampin**
- **Pyrazinamide**
- **Ethambutol**
- **Rifabutin***
- **Rifapentine**

Second-Line Drugs

- **Streptomycin**
- **Cycloserine**
- **p-Aminosalicylic acid**
- **Ethionamide**
- **Amikacin or kanamycin***
- **Capreomycin**
- **Levofloxacin***
- **Moxifloxacin***

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

Treatment Regimens

- **Four regimens recommended for treatment of culture-positive TB, with different options for dosing intervals in continuation phase**
- **Initial phase: standard four drug regimens (INH, RIF, PZA, EMB), for 2 months**
- **Continuation phase: additional 4 months or (7 months for some patients)**

Why 4 drugs?

- **Combination of drugs needed over sufficient time**
  - Kill the TB bacilli rapidly
  - Prevent the emergence of drug resistance
  - Eliminate persistent bacilli to prevent relapse or failure
- **Drugs differ in their activity against TB**
  - Bactericidal
  - Bacteriostatic

Bactericidal

- **Ability of drug to rapidly kill multiplying *M. tb***
- **Drugs that have early bactericidal activity reduce the chance of resistance developing**
  - INH > EMB > RIF
  - PZA is poor in this regard

Bacteriostatic

- **Ability of drug to kill bacilli, mainly in the subpopulations of *M.tb,* that persist beyond the early months of therapy**
  - RIF and PZA have the greatest sterilizing activity followed by INH and SM
  - Sterilizing activity of RIF persists throughout the course of therapy but the same is not true for PZA

Why DOT?

- **DOT enables early identification of non-adherence, adverse drug reactions, and clinical worsening of TB**
- **Can lead to reductions in relapse and acquired drug resistance**

DOT
Impact on Completion Rates

• **Non-supervised therapy (n=9)**	**61%**
• **Modified DOT (n=2)**	**79%**
• **DOT (n=4)**	**86%**
• **Enhanced DOT (n=12)**	**91%**

DOT = Directly Observed Therapy
Modified DOT = DOT given only for a portion of the treatment period, often while the patient was hospitalized
Enhanced DOT = Individualized incentives & enablers were provided in addition to DOT

JAMA 1998;279:943-948

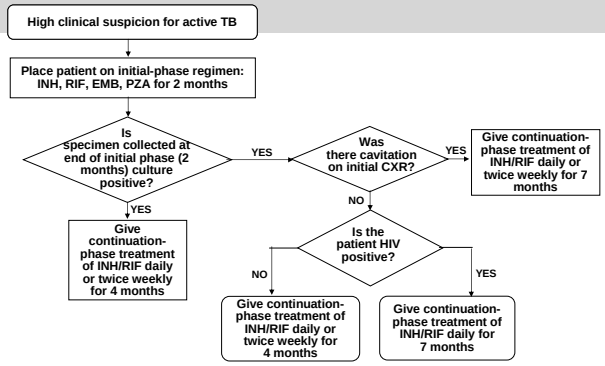
Why Extend Continuation-Phase Treatment for 3 Months?

- **Cavitary disease and positive sputum culture at 2 months associated with increased relapse in clinical trials**
- **Extended continuation phase decreased relapses in silicotuberculosis (from 20% to 3%)**

When to Extend Continuation-Phase Treatment for 3 Months?

- **Cavitary pulmonary disease and positive sputum cultures at completion of initial phase**
- **Once-weekly INH and rifapentine started in continuation phase and sputum specimen collected at the end of initial phase is culture positive**
- **HIV-infected with positive 2-month sputum culture**
- **Initial phase excluded PZA**

Duration of Continuation-Phase Treatment for Culture(+) TB



Treatment of Culture (+) TB – 1

(Rated: AI in HIV-negative, AII in HIV-positive patients)

Initial Phase

2 months - INH, RIF, PZA, EMB daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 4 months - INH, RIF daily (126 doses, within 18 weeks)
2) 4 months - INH, RIF twice / week (36 doses, within 18 weeks)
3) 7 months - INH, RIF daily (217 doses, within 31 weeks)*
4) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*

* Continuation phase increased to 7 months if initial chest x-ray shows cavitation and specimen collected at end of initial phase (2 months) is culture positive

Treatment of Culture (+) TB – 2

Regimens without Pyrazinamide
(Rated: CI for HIV-negative, CII for HIV-positive patients)

Initial Phase

2 months - INH, RIF, EMB daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 7 months - INH, RIF daily (217 doses, within 31 weeks)
2) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*

* Twice weekly dosing is not recommended for persons with CD4+ T-lymphocytes cell count < 100/µl

Treatment of Culture (–) TB*

Initial Phase

2 months - INH, RIF, EMB, PZA daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 2 months - INH, RIF daily (56 doses, within 8 weeks)
2) 2 months - INH, RIF twice / week (16 doses, within 8 weeks)

* All cultures are negative, but evaluation at 2 months reveals clinical and chest x-ray response to antituberculosis drug therapy

Treatment Monitoring – 1

- **Monthly sputum for AFB smear and culture (until 2 consecutive cultures negative)**
- **Serial sputum smears every 2 weeks to assess early response**
- **Additional drug-susceptibility tests if culture-positive after 3 months of treatment**

Treatment Monitoring – 2

- **Periodic (minimum monthly) evaluation to assess adherence and identify adverse reactions**
- **Repeat chest x-ray:**
  - At completion of initial treatment phase for patients with initial negative cultures
  - At end of treatment for patients with culture-negative TB
  - Generally not necessary for patients with culture positive TB
- **Renal function, AST, ALT, bilirubin, and platelet count if abnormalities at baseline**
- **Visual acuity and color vision monthly if EMB used > 2 months or doses > 15-20 mg/kg**

Special Treatment Situations
Extrapulmonary TB

- **Similar treatment regimen for pulmonary TB***
- **6 to 9 month regimens that include INH and RIF are effective**
- **Corticosteroids used as adjunctive therapy for patients with TB meningitis and pericarditis**
- **If PZA cannot be used in the initial phase, continuation phase must be increased to 7 months**

* Except for central nervous system (CNS) TB, including meningitis; length of therapy is 9-12 months

Special Treatment Situations
Pregnancy and Breastfeeding

- **Untreated TB represents greater hazard to a woman and her child than treatment of disease**
- **Treatment of pregnant woman with suspected TB should be started if probability of TB is moderate to high**
- **Initial phase treatment regimen should consist of INH, RIF, and EMB**
  - SM should not be substituted for EMB because of possible teratogenic effects
  - PZA not generally recommended for pregnant women in the United States

Special Treatment Situations
Renal Insufficiency & End-Stage Renal Disease

- **Renal insufficiency complicates management of TB because some anti-TB medications are cleared by the kidneys**
- **Dosage should not be decreased because peak serum concentrations may be too low; smaller doses may decrease drug efficacy**
- **Dosing interval of anti-TB drugs should be increased**
- **Most drugs can be given 3 times weekly after hemodialysis**
  - Dose must be adjusted for some drugs

Special Treatment Situations
Hepatic Disease (1)

- **Choose regimens with fewer hepatotoxic agents for patients with liver disease**
- **<u>Recommended regimens:</u>**
  1) Treatment without PZA
     Initial phase (2 months): INH, RIF, and EMB
     Continuation phase (7 months): INH and RIF
  2) Treatment without INH
     Initial phase (2 months): RIF, PZA, and EMB
     Continuation phase (4 months): RIF, EMB, and PZA

Special Treatment Situations
Hepatic Disease (2)

- **<u>Recommended regimens:</u> (continued)**

3) Regimens with only one potentially hepatotoxic drug
   - RIF should be retained
   - Duration of treatment is 12-18 months

4) Regimens with no potentially hepatotoxic drugs
   - Duration of treatment is 18-24 months

Treatment Guidelines
Available Online

- **CDC's Morbidity and Mortality Weekly Report: http://www.cdc.gov/mmwr**
- **American Thoracic Society:**

http://www.thoracic.org/adobe/statements/treattb.pdf

Additional TB Resources

For additional information on tuberculosis, visit the Division of Tuberculosis Elimination Web site at:

http://www.cdc.gov/tb

NEW JERSEY MEDICAL SCHOOL

INFORMATION LINE

1•800•4TB•DOCS (482-3627)
www.umdnj.edu/globaltb