



Tuberculosis Diagnosis, Treatment, and Special Situations

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TB Diagnosis

“The first rule of TB diagnosis: is to think TB....”

Diagnosis of Pulmonary TB

(80-85% of TB Cases)

- Chest x-ray
 - Standard PA and lateral films; apical lordotic views may be helpful
 - Infiltrates, nodular densities, cavities, +/- hilar adenopathy
 - Abnormalities may be subtle in immunocompromised patients
 - Previous x-rays for comparison may be useful
- CT scans
 - Often obtained
 - Nice to have but rarely critical to diagnosis
 - Expensive

Diagnosis of Pulmonary TB

- TST
 - Positive supports but does not make diagnosis
 - Negative does not exclude TB as possible diagnosis
- Quantiferon
 - Screening test only, not diagnostic

Diagnosis of Pulmonary TB

- Mycobacteriology laboratory tests
 - AFB smear
 - MTD – NAA
 - Preliminary results
 - Beware!
 - Culture
 - ID of isolate – confirm *M.tb*
 - Antimicrobial susceptibility testing

Diagnosis of Pulmonary TB

- Coughed sputum
 - Best specimen when available
 - Early AM best, supervise collection
 - AFB smear best available tool for assessing infectiousness
 - Most likely to yield positive culture
 - Multiple specimens recommended to maximize chances for +AFB/culture

Yield of smear and culture for the diagnosis of pulmonary tuberculosis

Induced sputum (% yield)

specimen	one	two	three	four
AFB smear	64	81	91	98
AFB culture	70	91	99	100

Int J Tuberc Lung Dis. 2001 Sep;5(9):855-60. Al Zahrani K, et al.

Treatment of Pulmonary vs. Extra-Pulmonary TB

- Same drugs, same doses, duration of treatment may vary
- Prospects for survival, cure similar; permanent damage depends on location of infection
- Guidelines for monitoring (drug side effects/toxicity) similar
- Guidelines for supervision of treatment (DOT) similar – less strict for extra-pulmonary because usually not infectious

Treatment of TB Disease

- The “enough” rules
 - Enough drugs
 - Enough medication
 - Long enough
- Generally two types of errors
 - Failure to prescribe correct regimen
 - Failure of patient to adhere to regimen
- Appropriate case management and DOT can lessen risk of developing drug resistance

Treatment Pearls

- Ethambutol can be discontinued once susceptibility to INH and RIF demonstrated
- PZA must be continued for full recommended course to qualify for short-course treatment
- DOT standard of care for all – **extremely important for co-infected**
- Sputum collection at end of first 2 months of treatment essential

Antituberculosis Drugs Currently in Use in the US

○ First-line Drugs

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

○ Second-line Drugs

- Cycloserine
- Ethionamide
- Levofloxacin
- Moxifloxacin
- Gatifloxacin
- *P*-Aminosalicylic acid
- Streptomycin
- Amikacin/kanamycin
- Capreomycin
- Linezolid

Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 1

- Initial phase
 - INH/RIF/PZA/EMB
 - 7 d/wk for 56 doses (8 weeks)
 - Option – 5 d/wk for 40 doses (8weeks)
- Continuation phase
 - INH/RIF
 - 7 d/wk for 126 doses (18 weeks)
 - 5 d/wk for 90 doses (18 weeks)
 - Twice weekly for 36 doses (18 weeks)*
 - INH/RPT
 - Once weekly for 18 doses (18 weeks)*

Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 2

- Initial phase
 - INH/RIF/PZA/EMB
 - 7 d/wk for 14 doses (2 weeks)
 - Then twice weekly for 12 doses (6 weeks) *
 - OR
 - 5 d/wk for 10 doses (2 weeks)
 - Then twice weekly for 12 doses (6 weeks)*
- Continuation phase
 - INH/RIF
 - Twice weekly for 36 doses (18 weeks)*
 - INH/RPT
 - Weekly for 18 doses*

Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 3

- Initial phase
 - INH/RIF/PZA/EMB
 - Three times weekly for 24 doses (8 weeks)
- Continuation phase
 - INH/RIF
 - Three times weekly for 54 doses (18 weeks)

Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 4

- Initial phase
 - INH/RIF/EMB
 - 7 d/wk for 56 doses (8 weeks)
 - or
 - 5 d/wk for 40 doses (8 weeks)
- Continuation phase
 - INH/RIF
 - 7 d/wk for

When to Extend Continuation Phase of Treatment

- (from 2 drugs x 4 months to 2 drugs x 7 months)
- Recommended for patients with cavitory pulmonary disease **and** positive 2-month sputum culture
 - Extension may be considered if either factor is present
- Initial phase did not include PZA

Treatment Monitoring (1)

- Periodic (minimum monthly) clinical evaluation to assess adherence and identify adverse reactions
- Bacteriologic monitoring
 - Sputum smears every 2 weeks to assess early response until smear negative
 - After converted to smear negative, monthly sputum clusters until culture negative



Treatment Monitoring (3)

- Visual acuity and color vision monthly if EMB used

Common Adverse Reactions to Drug Treatment (1)

Caused by	Adverse Reaction	Signs and Symptoms
Any drug	Allergy	Skin rash
Ethambutol	Eye damage	Blurred or changed vision Changed color vision
Isoniazid, Pyrazinamide, or Rifampin	Hepatitis	Abdominal pain Abnormal liver function test results Fatigue Lack of appetite Nausea / Vomiting Yellowish skin or eyes Dark urine

Common Adverse Reactions to Drug Treatment (2)

Caused by	Adverse Reaction	Signs and Symptoms
Isoniazid	Peripheral neuropathy	Tingling sensation in hands and feet
Pyrazinamide	Gastrointestinal intolerance Arthralgia Arthritis	Upset stomach, vomiting, lack of appetite Joint aches Gout (rare)
Injectibles	Ear damage Kidney damage	Balance problems Hearing loss Ringing in the ears Abnormal kidney function test results

Common Adverse Reactions to Drug Treatment (3)

Caused by	Adverse Reaction	Signs and Symptoms
Rifamycins Rifabutin Rifapentine Rifampin	Thrombocytopenia Gastrointestinal intolerance Drug interactions	Easy bruising Slow blood clotting Upset stomach Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment

Drug Interactions

- Some drug interactions change concentrations of antituberculosis drugs
- Antituberculosis drugs can change concentrations of other drugs
 - Rifamycins can decrease serum concentrations of some drugs used in treatment of HIV
 - Isoniazid increases concentrations of some drugs (e.g., phenytoin) to toxic levels
- Complete drug history of all prescription, OTC, and herbals essential part of treatment process

Drug Resistance (1)

- Established only by drug-susceptibility testing
- DOT is mandatory for all patients with drug resistant disease
- Treatment for drug resistant TB disease is dependent on susceptibility patterns of the specific organism

Special Treatment Situations

Extrapulmonary TB

- Similar treatment regimen for pulmonary TB*
- 6- to 9-month regimens that include INH and RIF are effective
- Corticosteroids sometimes used 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: Renal Insufficiency and End-Stage - Renal Disease

- Renal insufficiency complicates management of TB because some antituberculosis 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

Special Treatment Situations: Renal Insufficiency and End-Stage Renal Disease

- Dosing interval of antituberculosis drugs should be increased
- Most drugs can be given 3 times weekly after hemodialysis; for some drugs, dose must be adjusted

Special Treatment Situations

Hepatic Disease (1)

- May need to consider regimens with fewer hepatotoxic agents for patients with liver disease
- Recommended regimens:
 - 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)

- Recommended regimens: (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



TB & HIV Infection

- Risk factor of greatest significance for progression to active disease
- AIDS defining diagnosis
- Progression is preventable !!

Special Treatment Situations

HIV/AIDS

- Treatment for HIV-positive patients same as for HIV-negative patients, except
 - 1) Once-weekly INH-rifapentine in continuation phase is contraindicated in HIV-positive patients
 - 2) Twice-weekly INH-RIF or INH-rifabutin should not be used in patients with CD4+ T-lymphocyte counts less than 100/ μ l
- Every effort should be made to use a rifamycin-based regimen for the entire course of therapy



Effect of HIV on TB Infection

- HIV infection increases risk of TB disease by 100 fold
- Detection may be difficult in some patients
- Non-classical CXR presentation
- TB & anti- HIV therapies can interact negatively and cancel each other out



Effect of TB on HIV

- Increases HIV replications – higher viral load
- Decreases CD4 counts
- Higher risk of opportunistic infections & death
- Exacerbates weight loss & wasting
- Complicates treatment regimens

Challenge of Co-infection with HIV & TB

- Absorption of anti-TB drugs
- HAART & TB drug interactions

Treatment in special populations: Children

- Children
 - Same as adults
 - Doses based on weight
 - Fewer problems with toxicity
 - Harder to administer
 - Harder to monitor
 - Pills (crushed) vs. liquid preparations
 - Some clinicians reluctant to use ethambutol



Treatment in Special Populations: Pregnancy

- 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

Treatment in Special Populations: Pregnancy

- Initial phase treatment regimen should consist of INH, RIF, and EMB
- PZA not generally recommended for pregnant women in the United States
- SM should not be substituted for EMB because of possible teratogenic effects

Other Medication Issues

- Difficulty swallowing pills
 - Patient may not tell you
 - Crushed pills, administered in small amt food ok
- GI side effects (IREZ)
 - Nausea, anorexia common - usually can continue treatment – can be sign/symptom of hepatitis
 - Diarrhea less common but potentially important – can be marker for malabsorption, low blood/tissue drug levels

Side Effects vs. Toxicity

- Read (and re-read) drug sections of Treatment Guidelines (CDC/IDSA guidelines and Curry Center guidelines for drug resistant TB)
 - Section on each drug
 - Drug-drug interactions (table of rifamycin interactions w/ other drugs)
 - Make patient and family aware of side-effects
 - Consider copying info on drugs



Side Effects vs. Toxicity

- Observe and question patient, and document findings at each encounter
- Obtain LFTs and other screening tests at recommended intervals
- ORW, PHNs, HCPs should review case prn new symptoms and/or abnormal lab results, and at regular intervals



QUESTIONS?