Treatment of Tuberculosis Disease

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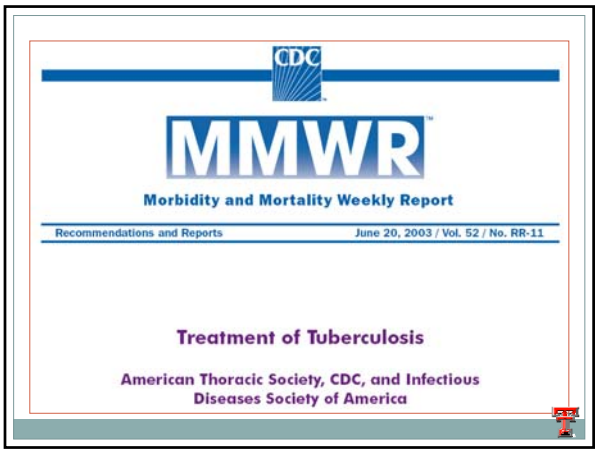
TB Updates for the Community: Partnering to Eliminate TB July 23, 2009

Objectives

- Review treatment guidelines
- Monitoring during therapy
- Adverse effects
- HIV, pregnancy, renal failure

Treatment Guidelines



Tenets of Therapy

- 6 months *minimum* treatment
- Multidrug therapy
- Directly observed therapy (DOT)

Current Drugs Available

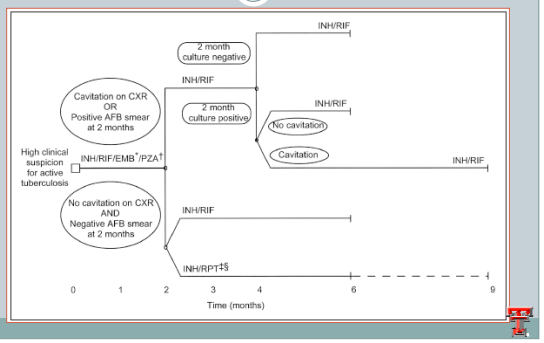
- First Line Drugs
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide
- Second Line Drugs
  - Cycloserine
  - Ethionamide
  - Levofloxacin*
  - Moxifloxacin*
  - Gatifloxacin*
  - p-Aminosalicylic acid
  - Streptomycin
  - Amikacin/kanamycin*
  - Capreomycin

Regimens

TABLE 2. Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms

Initial phase			Continuation phase			Range of total doses (minimal duration)	Rating* (evidence)†	
Regimen	Drugs	Interval and doses‡ (minimal duration)	Regimen	Drugs	Interval and doses‡§ (minimal duration)		HIV−	HIV+
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a	INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 56 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)*
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk),¶ then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)*
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a	INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

Treatment Algorithm



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

Monitoring During Drug Therapy

Monitoring

- Baseline Testing
  - **SPUTUM!!!**
  - HIV Testing
  - Liver Enzymes
  - Creatinine
  - Platelet Count
  - Visual Testing if on Ethambutol

Monitoring

- Follow-up monitoring
  - Repeat sputum stains and cultures monthly until negative
  - Repeat liver enzymes in high risk patients
  - Consider repeat platelet and creatinine in patients with baseline abnormalities
  - Toxicity screening

Adverse Events

Adverse Events

- Isoniazid (INH)
  - Asymptomatic transaminitis (10%-20%)
  - Hepatitis

TABLE 10. Clinical hepatitis in persons taking isoniazid and rifampin*

Drug	Number of studies	Patients	Clinical Hepatitis (%)
INH	6	38,257	0.6
INH plus other drugs but *not* RIF	10	2,053	1.6
INH plus RIF	19	6,155	2.7
RIF plus other drugs but *not* INH	5	1,264	1.1

Definition of abbreviations: INH = Isoniazid; RIF = rifampin.
* **Source:** Steele MA, Burk RF, Des Prez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest 1991;99:465–471. Reprinted with permission.

Adverse Events

- Isoniazid (INH)
  - Asymptomatic transaminitis (10%-20%)
  - Hepatitis (0.6%-2.7%)
  - Peripheral neuropathy (0.2%)
  - Lupus-like syndrome (1%)
  - Hypersensitivity reaction (rare)
  - Diarrhea (with liquid formulation)

Adverse Events

- Rifampin
  - Pruritic rash (6%)
  - GI upset
  - Myalgias (0.5%)
  - Hepatitis
  - Orange discoloration of body fluids (100%)

Adverse Events

- Pyrazinamide
  - Hepatotoxicity (1%?)
  - GI upset (common)
  - Arthralgia (40%)
  - Gouty arthritis (in predisposed patients)
  - Photosensitivity dermatitis

Adverse Events

- Ethambutol (EMB)
  - Retrobulbar neuritis
  - Peripheral neuropathy (rare)
  - Rash (<0.7%)

Special Situations

Active TB in HIV

- Same as HIV negative *except…*
- If CD4+ <100/ul
  - Daily or 3x/week therapy in continuation phase
- Immune reconstitution syndrome
  - May delay initiation of anti-retroviral therapy for few weeks
- DRUG INTERACTIONS!

Active TB in Pregnancy

- Risk of untreated TB usually outweighs risk of therapy
  - INH
  - Rifampin
  - Ethambutol
  - (Pyrazinamide)
- 9 months of therapy if no PZA
- Pyridoxine supplementation

Active TB in Renal Failure

TABLE 15. Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750–1,000 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week*
Ethionamide	No change	250–500 mg/dose daily
p-Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily)

Active TB in Severe Liver Disease

- Treatment without INH
  - Rifampin, PZA, EMB for 6 months
- Treatment without PZA
  - INH, Rifampin, EMB for **9** months
- Treatment with only one hepatotoxic agent
  - Rifampin plus 2 second line drugs for 12-18 months
- Treatment with no hepatotoxic agents
  - 4 drug therapy (which?) for up to 2 years

Multidrug Resistant TB

TABLE 15. Potential regimens for the management of patients with drug-resistant pulmonary tuberculosis

Pattern of drug resistance	Suggested regimen	Duration of treatment (mo)	Comments
INH (± SM)	RIF, PZA, EMB (an FQN may strengthen the regimen for patients with extensive disease)	6	In BMRC trials, 6-mo regimens have yielded ≥95% success rates despite resistance to INH if four drugs were used in the initial phase and RIF plus EMB or SM was used throughout.* Additional studies suggested that results were best if PZA was also used throughout the 6 mo (Rating BII).† Fluoroquinolones were not employed in BMRC studies, but may strengthen the regimen for patients with more extensive disease (Rating BIII). INH should be stopped in cases of INH resistance (see text for additional discussion).
INH and RIF (± SM)	FQN, PZA, EMB, IA, ± alternative agent	18–24	In such cases, extended treatment is needed to lessen the risk of relapse. In cases with extensive disease, the use of an additional agent (alternative agents) may be prudent to lessen the risk of failure and additional acquired drug resistance. Resectional surgery may be appropriate (see text).
INH, RIF (± SM), and EMB or PZA	FQN (EMB or PZA if active), IA, and two alternative agents	24	Use the first-line agents to which there is susceptibility. Add two or more alternative agents in case of extensive disease. Surgery should be considered (see text).
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 months (an IA may be included for the first 2–3 months for patients with extensive disease)	12–18	Daily and three times weekly regimens of INH, PZA, and SM given for 9 mo were effective in a BMRC trial‡ (Rating BI). However, extended use of an injectable agent may not be feasible. It is not known if EMB would be as effective as SM in these regimens. An all-oral regimen for 12–18 mo should be effective (Rating BIII). But for more extensive disease and/or to shorten duration (e.g., to 12 months), an injectable agent may be added in the initial 2 mo of therapy (Rating BIII).

Extensive-drug Resistant TB

- Call an expert

More Information

- www.cdc.gov
- “Treatment of Tuberculosis” MMWR, vol 52, June 2003