Treatment of Active Tuberculosis

Michael Lauzardo, MD MSc
Chief, Division of Infectious Diseases and Global Medicine
Southeastern National Tuberculosis Center
University of Florida
Treatment
“How the Battle Against TB was Won . . . and Almost Lost”

- 1944 – Streptomycin Introduced
- 1946 – Youmans recognizes SM resistance
- 1951 – Need for multi-drug therapy
- 1952 – PZA introduced
- 1952 – INH introduced
- 1961 – EMB introduced
- 1966 – Rifampin introduced

“The Lord hath created medicines out of the earth and he that is wise will not abhor them.”

- Waksman Noble Prize 1952
Introduction

• The treatment of TB disease requires combination therapy to avoid selecting naturally occurring resistant mutants.

• The initial combinations regimens were defined by what was available in the middle of the 20th century, namely, streptomycin, para-aminosalicylic acid, and isoniazid.

• As new drugs were developed, they were tested with older drugs until the current regimen of isoniazid, rifampin, and pyrazinamide (often with ethambutol as a fourth drug) was defined.
Introduction

- *M. tuberculosis* grows slowly.
- *M. tuberculosis* is generally classified into two subpopulations: those that are metabolically active and replicating, and those that are not.
- Typically, successful treatment regimens contain agents that act on both subpopulations.
- Persisting organisms are metabolically dormant and do not actively replicate; consequently, their elimination requires prolonged treatment duration.
- The ability of drugs to kill these persisting mycobacteria is called *sterilizing activity*. 
General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with innate resistance to antibiotic action
Development of Resistance

INH

RIF

INH

INH

INH

INH

RIF
General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with innate resistance to antibiotic action
- Slow or intermittent growth of mycobacterium which permits the persistence of viable organisms despite prolonged antibiotic treatment, because only actively replicating organisms are killed by antibiotics
Treatment of TB

- M.TB. exists in
  - Two states
    - Actively growing
    - Latent
  - Three environments
    - Inside macrophage
      - Intracellular
    - Extracellular
      - Often in pulmonary cavities
    - Inside granulomas
**TX of TB**

- **Site of activity of TB drugs**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EXTRA</th>
<th>MACRO</th>
<th>GRAN.</th>
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<tbody>
<tr>
<td>INH</td>
<td>++</td>
<td>+</td>
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<tr>
<td>RIF</td>
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<td>PZA</td>
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<td>EMB</td>
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<td>STM</td>
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TX of TB

- Initial treatment aimed at
  - Extracellular organisms
  - Sterilize sputum
  - Reduce infectivity

- Secondary treatment aimed at
  - Eradicating organism from
    - Macrophage
    - Granulomas
## TX of TB

<table>
<thead>
<tr>
<th></th>
<th>FIRST TWO MONTHS</th>
<th>FOUR MONTHS POST CONVERSION</th>
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<tbody>
<tr>
<td><strong>INH</strong></td>
<td>300 MG/D PO</td>
<td>300 MG/D</td>
</tr>
<tr>
<td><strong>RIF</strong></td>
<td>600 MG/D PO</td>
<td>600 MG/D</td>
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<tr>
<td><strong>PZA</strong></td>
<td>15-30 MG/KG/D PO</td>
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<tr>
<td><strong>EMB</strong></td>
<td>15-25 MG/KG/D PO</td>
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<tr>
<td><strong>STM</strong></td>
<td>1 GM/D IM</td>
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</table>
TB Treatment (CDC Guidelines 2003)

- Start with four drugs in all patients (in patients from areas where INH resistance exceeds > 4%) – Public Health Department has primary responsibility for treatment
  - INH, RIF, PZA and EMB or SM until sensitivities return
  - Once pansensitive, D/C EMB, after two months of therapy, D/C PZA
  - Continue INH and RIF for four more months for total of six months
- Must have culture conversion by two months (prolong therapy)
- Six month regimen good for HIV(-) and (+)
- Can use biw or tiw regimen
TB Treatment (CDC Guidelines 2003)

- Monitor adherence and toxicity
- DOT preferred, combination pills for self administered
- INH, rifampin, EMB safe in pregnancy, ?PZA (need nine months Rx w/o PZA)
- Corticosteroids for pericardial constriction, meningitis in children, ? role in endobronchial disease
- Culture negative ("clinical TB") – four months of therapy effective
ATS/CDC/IDSA
Treatment Guidelines 2003

- Responsibility for successful treatment is clearly assigned to the public health departments
- Strong recommendations for initial patient centered case management and DOT
- Recommend getting sputum cultures at two months to identify potential relapse
- Extended treatment for those still with positive cultures at two months and cavities on CXR
- Role for rifabutin, rifapentine and fluoroquinolones
- Treatment completion defined by number of doses as well as duration of therapy
Major Goals of TB Treatment

- Cure patient, minimize risk of death/disability, prevent transmission to others
- Provide safest, most effective therapy in shortest time
- Prescribe multiple drugs to which the organisms are susceptible
- Never treat with a single drug or add single drug to failing regimen
- Ensure adherence and completion of therapy
Develop Treatment and Monitoring Plan

Plan should include

- Description of treatment regimen
- Methods for assessing/ensuring adherence
- Monitoring methods for treatment response and adverse events
Adherence

- Nonadherence results in inadequate treatment
- Can lead to treatment failure, relapse, ongoing transmission, and drug resistance
- Clinician responsible for completion of therapy
- To ensure adherence, provide education, case management, DOT, incentives and enablers, and combination pills
- If these fail, take more restrictive action
Case Management

Strategy to ensure patients complete treatment. Three elements:

- Assigning responsibility
- Conducting regular systematic review
- Developing plans to address barriers to adherence

Case managers must ensure patients are educated about TB, therapy is continuous, and contacts are evaluated properly.
Directly Observed Therapy (DOT)

- Health-care worker watches patient swallow each dose
- DOT is preferred management strategy for all patients
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters
- For drug-resistant TB, use daily regimen and DOT
TB Disease Treatment Regimens

- Four regimens recommended for treatment of drug-susceptible TB, with different options for number of doses and for length of continuation phase
- Initial phase: standard four drugs (INH, RIF, PZA, EMB) for 2 months (one excludes PZA)
- Continuation phase: additional 4 months; 7 months for some patients
TB Disease Treatment Regimens (cont.)

- When to use 7-month continuation phase:
  - Disease is cavitary and sputum culture is positive at end of initial phase;
  - Initial phase excluded PZA; or
  - Once-weekly INH and RPT used in continuation phase, and culture is positive at end of initial phase.
Regimen 1 for Treatment of Pulmonary, Drug-Susceptible TB
6-Month Standard Regimen for Most Patients

Initial phase
INH, RIF, PZA, EMB daily (7 or 5 days/week) for 8 weeks

4-month continuation phase options
1) INH, RIF daily (7 or 5 days/week) for 18 weeks
2) INH, RIF intermittently (2 days/week or 1 day/week for INH, rifapentine) for 18 weeks
Regimen 2 for Treatment of Pulmonary, Drug-Susceptible TB
6-Month Daily + Intermittent Dosing Options

Initial phase
INH, RIF, PZA, EMB daily (7 or 5 days/week) for 2 weeks, then 2 days/week for 6 weeks

4-month continuation phase options
1) INH, RIF intermittently (2 days/week) for 18 weeks
2) INH, RPT intermittently (1 day/week) for 18 weeks
Regimen 3 for Treatment of Pulmonary, Drug-Susceptible TB
6-Month Intermittent Dosing Options

Initial phase
INH, RIF, PZA, EMB intermittently (3 days/week) for 8 weeks

4-month continuation phase
INH, RIF intermittently (3 days/week) for 18 weeks
Regimen 4 for Treatment of Pulmonary, Drug-Susceptible TB
7-Month Regimen without Pyrazinamide

Initial phase
INH, RIF, EMB daily (7 or 5 days/week) for 8 weeks

7-month continuation phase options
1) INH, RIF daily (7 or 5 days/week) for 31 weeks
2) INH, RIF intermittently (2 days/week) for 31 weeks
Treatment Completion

- Defined as ingesting prescribed number of doses within specified time
- Duration depends on drugs used, isolate’s susceptibility, and patient’s response to drugs
- Most patients can be treated with 6-mo or 9-mo therapy; 6 mo is used for most patients
## Patient Monitoring

### Recommended Examinations for Baseline Monitoring

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended Test</th>
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<tbody>
<tr>
<td>All patients</td>
<td>Measure aminotransferases (i.e., AST, ALT), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count</td>
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<tr>
<td>Patients at risk for hepatitis B or C (e.g., injection drug user, born in Asia or , or HIV infected)</td>
<td>Conduct serologic tests</td>
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<tr>
<td>Patients who are taking EMB</td>
<td>Test visual acuity (Snellen chart) and color vision (Ishihara)</td>
</tr>
<tr>
<td>HIV-infected patients</td>
<td>Obtain CD4+ lymphocyte count</td>
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## Patient Monitoring (cont.)
### Monitoring During Treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Repeat at least monthly clinical evaluations to</td>
</tr>
<tr>
<td></td>
<td>• Identify possible adverse reactions to medications</td>
</tr>
<tr>
<td></td>
<td>• Assess adherence</td>
</tr>
<tr>
<td>Patients who are taking EMB</td>
<td>• Question monthly regarding visual disturbances</td>
</tr>
<tr>
<td></td>
<td>• Repeat monthly testing for visual acuity (Snellen chart) and color vision (Ishihara) for patients whose dose exceeds 15-20 mg/kg and those who have been receiving EMB for &gt;2 months</td>
</tr>
<tr>
<td>Patients who have extrapulmonary TB disease</td>
<td>Evaluation depends on</td>
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<tr>
<td></td>
<td>• Sites involved</td>
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<td></td>
<td>• Ease with which specimens can be obtained</td>
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Evaluating Response to Treatment

- Assess patient’s response to treatment using three methods:
  - Clinical evaluation, bacteriological examination, chest radiograph
- Conduct clinical evaluations at least monthly; after 2 months of therapy, if symptoms do not resolve, reevaluate for
  - Potential drug-resistant disease
  - Nonadherence to drug regimen
Evaluating Response to Treatment (cont.)

- Bacteriological examination
  If cultures do not convert to negative after 3 months of therapy, evaluate patient for drug resistance or adherence issues; after 4 months, consider treatment failed

- Chest radiograph
  Patients with initially negative cultures should have chest radiograph after 2 months of treatment and at completion of therapy
Evaluating Response to Treatment (cont.)

- Monitor for adverse reactions
- Common adverse reactions include
  - Gastrointestinal problems
  - Hepatitis
  - Rash
  - Fever
Case Discussion: 62 year old woman with a history of alcohol abuse
Causes of Inadequate Response to Therapy

- Non-adherence
  - DOT
  - Involuntary detention
- Increased drug resistance/incorrect sensitivities
- Malabsorption/increased metabolism
- Inability of drugs to penetrate affected tissues
First Line Drugs

- More effective
  - Bacteriocidal vs. Static
  - Higher PK/MIC ratio
- More experience
- Lower incidence of adverse drug reactions (ADR)
- Less expensive
- Easier to administer
Isoniazid
Isoniazid

- Isoniazid (INH) is a first-line agent for treatment of all forms of tuberculosis caused by organisms known or presumed to be susceptible to the drug. It has profound early bactericidal activity against rapidly dividing cells.

- **Adults (maximum):** 5 mg/kg (300 mg) daily; 15 mg/kg (900 mg) once, twice, or three times weekly.

- **Children (maximum):** 10–15 mg/kg (300 mg) daily; 20–30 mg/kg (900 mg) twice weekly.

- **Preparations.** Tablets (50 mg, 100 mg, 300 mg); syrup (50 mg/5 ml); aqueous solution (100 mg/ml) for intravenous or intramuscular injection.
Isoniazid Adverse Effects

- **Asymptomatic elevation of aminotransferases**: Elevations up to five times the upper limit of normal occur in 10--20% of persons receiving INH alone for LTBI.
- **Clinical hepatitis**: Hepatitis occurred in only 0.1--0.15% of 11,141 persons receiving INH alone as treatment for latent tuberculosis infection in an urban tuberculosis control program.
- In the meta-analysis the rate of clinical hepatitis was 1.6% when INH was given with other agents, not including RIF, the risk was higher when the drug was combined with RIF, an average of 2.7% in 19 reports.
Isoniazid Adverse Effects

- **Fatal hepatitis:** A large survey estimated the rate of fatal hepatitis to be 0.023%.
  - The risk may be increased in women.
  - Death has been associated with continued administration of INH despite onset of symptoms of hepatitis.

- **Peripheral neurotoxicity:** This adverse effect is dose related and is uncommon (less than 0.2%). The risk is increased in persons with other conditions that may be associated with neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and breastfeeding women.
Isoniazid Adverse Effects

- **Central nervous system effects**: Effects such as dysarthria, irritability, seizures, dysphoria, and inability to concentrate.
- **Lupus-like syndrome**: Approximately 20% of patients receiving INH develop anti-nuclear antibodies. Less than 1% develop clinical lupus erythematosus.
- **Hypersensitivity reactions**
- **Monoamine (histamine/tyramine) poisoning**: This has been reported to occur after ingestion of foods and beverages with high monoamine content but is rare.
- **Diarrhea**: Use of the commercial liquid preparation of INH, because it contains sorbitol, is associated with diarrhea.
INH

• Bacteriocidal

• Mechanism of Action (MOA)
  – Decreases DNA synthesis
  – Interferes with various enzymes
    • Mycolic acid synthesis for cell wall
  – Enhances permeability of other drugs

• Spectrum
  – M. TB only
    • Rapidly growing
INH Drug Interactions

• INH
  – Phenytoin
  – Theophylline
  – Warfarin
  – Benzodiazepines
  – Cycloserine
Rifampin (RIF) is a first-line agent for treatment caused by organisms with known or presumed sensitivity to the drug. It has activity against organisms that are dividing rapidly (early bactericidal activity) and against semidormant bacterial populations, thus accounting for its sterilizing activity. Rifampin is an essential component of all short-course regimens.

**Adults (maximum):** 10 mg/kg (600 mg) once daily, twice weekly, or three times weekly.

**Children (maximum):** 10--20 mg/kg (600 mg) once daily or twice weekly.

Preparations. Capsules (150 mg, 300 mg); contents of capsule may also be mixed in an appropriate diluent to prepare an oral suspension; aqueous solution for parenteral administration.
Rifampin Adverse Effects

- **Cutaneous reactions:** Pruritis with or without rash may occur in as many as 6% of patients but is generally self-limited. More severe, true hypersensitivity reactions are uncommon, occurring in 0.07--0.3% of patients.

- **Gastrointestinal reactions**

- **Flulike syndrome:** This may occur in 0.4--0.7% of patients receiving 600 mg twice weekly but not with daily.

- **Hepatotoxicity:** Transient asymptomatic hyperbilirubinemia may occur in as many as 0.6% of patients receiving the drug. More severe clinical hepatitis that, typically, has a cholestatic pattern may also occur.
Rifampin Adverse Effects

- Severe immunologic reactions: In addition to cutaneous reactions and flulike syndrome, other reactions thought to be immune mediated include the following: thrombocytopenia, hemolytic anemia, acute renal failure, and thrombotic thrombocytopenic purpura. These reactions are rare, each occurring in less than 0.1% of patients.

- Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be warned of this effect at the time treatment is begun. Soft contact lenses and clothing may be permanently stained.
Rifampin Adverse Effects

- **Drug interactions due to induction of hepatic microsomal enzymes:** There are a number of drug interactions with potentially serious consequences.
- Of particular concern are reductions, often to ineffective levels, in serum concentrations of common drugs, such as oral contraceptives, methadone, and warfarin.
- In addition there are important bidirectional interactions between rifamycins and antiretroviral agents.
- Because information regarding rifamycin drug interactions is evolving rapidly, readers are advised to consult the CDC website [www.cdc.gov/nchstp/tb/](http://www.cdc.gov/nchstp/tb/) to obtain the most up-to-date information or [http://hivinsite.ucsf.edu/arvdb?page=ar-00-02](http://hivinsite.ucsf.edu/arvdb?page=ar-00-02).
Rifampin

- Bacteriocidal
- Mechanism of Action
  - Inhibits DNA dependent RNA synthesis
- Spectrum
  - M. TB, Non-tuberculous mycobacteria species
  - Rapid and slow growing
  - Staph, legionella, meningococcal meningitis, mrsa
  - Gram negative organisms: KLEB., E.Coli, shigella
RIFAMPIN

• Dose
  – Child: 10 – 20 mg/kg/day
  – Adult: 10 mg/kg/d, nmt 600 mg/day given qd, biw, or tiw

• Adverse Drug Reactions
  – GI – anorexia, diarrhea, dysphagia
  – Rash, pruritis (6%)
  – Arthralgias, myalgias
  – Hepatic
    • Hyperbilirubinemia – 0.6%
    • Hepatitis – 0% alone, 2.7% w. INH,
  – Thrombocytopenia < 0.1%
  – Decreased thyroid, adrenal, VIT D, etc.
Rifampin Drug Interactions

- Oral Anticoagulants
- Benzodiazepines
- Methadone
- Oral Contraceptives
- Sulfonylureas
- Theophylline
- levothyroxine

- Ca channel blockers (dilt., nifed, verap)
- Beta-blockers
- HIV-PI
- Phenytoin
- Methadone
- Sulfonylureas
- levothyroxine
Rifabutin

- Rifabutin is used as a substitute for RIF in the treatment of all forms of tuberculosis.
- The drug is generally reserved for patients who are receiving any medication having unacceptable interactions with rifampin or have experienced intolerance to rifampin.
- **Adults (maximum):** 5 mg/kg (300 mg) daily, twice, or three times weekly. The dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors. ([http://www.cdc.gov/nchstp/tb/](http://www.cdc.gov/nchstp/tb/), to obtain the most up-to-date information.)
- **Children:** Appropriate dosing is unknown
Rifabutin Adverse Effects

- **Hematologic toxicity:**
  - In a placebo-controlled, double-blind trial involving patients with advanced acquired immunodeficiency syndrome (AIDS) (CD4+ cell counts <200 cells/µl), neutropenia occurred in 25% compared with 20% in patients receiving placebo (p = 0.03).
  - Neutropenia severe enough to necessitate discontinuation of the drug occurred in 2% of patients receiving the drug.
  - The effect is dose related, occurring more frequently with daily than with intermittent administration of the same dose.
  - In several studies of patients with and without HIV infection, neither neutropenia nor thrombocytopenia was associated with rifabutin.
Rifabutin Adverse Effects

- **Uveitis:** This is a rare (less than 0.01%) complication when the drug is given alone at a standard (300 mg daily) dose. The occurrence is higher (8%) with higher doses or when used in combination with macrolide antimicrobial agents.

- **Gastrointestinal symptoms:** These symptoms occurred in 3% of patients with advanced HIV infection given 300 mg/day.

- **Other less common effects:**
  - Polyarthralgias,
  - Hepatotoxicity,
  - Pseudojaundice,
  - Rash,
  - Flulike syndrome:
Rifabutin

- Trade name: Mycobutin
- Derivative of rifampin
- Approved for prevention of Mycobacterium avium complex
- Trials for prevention of MTB began in February of 1995
- Interferes with DNA synthesis
- Bactericidal or bacteriostatic
Rifabutin

- Discolors body fluids
- Cross-hypersensitivity with rifampin
- Cross-resistance with rifampin
- Less hepatic effect than RIF
- Less potent enzyme inducer than RIF
Rifabutin

- ADR
  - Neutropenia – dose-related
  - Hepatitis < 1%
  - Rash < 0.1%
  - Flu-like syndrome < 0.1%
  - Uveitis
    - 8% at higher doses, macrolides, PI
Pyrazinamide (PZA)

- **Role in treatment regimen.** Pyrazinamide (PZA) is a first-line agent for the treatment of all forms of tuberculosis caused by organisms with known or presumed susceptibility to the drug. The drug is believed to exert greatest activity against the population of dormant or semi-dormant organisms contained within macrophages or the acidic environment of caseous foci (54).

- **Adults:** 20–25 mg/kg per day.

- **Children (maximum):** 15–30 mg/kg (2.0 g) daily; 50 mg/kg twice weekly (2.0 g).

- **Preparations.** Tablets (500 mg, scored).
Pyrazinamide
PZA Adverse Effects

- **Hepatotoxicity**: Early studies using doses of 40--70 mg/kg per day reported high rates of hepatotoxicity.
- However, in treatment trials with multiple other drugs, including INH, liver toxicity has been rare at doses of 25 mg/kg per day or less.
- In one study, however, hepatotoxicity attributable to PZA used in standard doses occurred at a rate of about 1%.
- **Gastrointestinal symptoms (nausea, vomiting)**: Mild anorexia and nausea are common at standard doses.
- Vomiting and severe nausea are rare except at high doses.
PZA Adverse Effects

- **Nongouty polyarthralgia:** Polyarthralgias may occur in up to 40% of patients receiving daily doses of PZA. In clinical trials of PZA in the initial intensive phase of treatment, arthralgias were not noted to be a significant problem.

- **Asymptomatic hyperuricemia:** This is an expected effect of the drug and is generally without adverse consequence.

- **Acute gouty arthritis:** Acute gout is rare except in patients with preexisting gout, generally a contraindication to the use of the drug.

- **Transient morbilliform rash:** This is usually self-limited and is not an indication for discontinuation of the drug.

- **Dermatitis:** PZA may cause photosensitive dermatitis.
Pyrazinamide

- Bacteriocidal
- Mechanism of Action: ??
- Spectrum
  - M.TB only – requires acid medium
  - Penetrates cell wall well
    - Intracellular and caseus foci
    - Slow growing organisms
PZA

• Dose
  – 15-30 mg/kg qd
  – 50-70 mg/kg/day biw or tiw
    • Max dose: 2 gm qd, 3 gm tiw, 4 gm biw

• Adverse Drug Reaction
  – Rash, photosensitive dermatitis
  – Elevated uric acid, pyrazinoic acid
  – Hepatotoxicity ~ 1% doses > 25mg/kg
  – Polyarthralgias – 40%
  – Exacerbates diabetes
PZA

- Monitor
  - Liver function
  - Uric acid levels
  - Renal function
Ethambutol
Ethambutol

- **Role in treatment regimen.** Ethambutol (EMB) is a first-line drug for treating all forms of tuberculosis. It is included in initial treatment regimens primarily to prevent emergence of RIF resistance when primary resistance to INH may be present.

- **Adults:** 15–20 mg/kg per day:

- **Children (maximum):** 15–20 mg/kg per day (2.5 g); 50 mg/kg twice weekly (2.5 g). The drug can be used safely in older children but should be used with caution in children in whom visual acuity cannot be monitored

- **Preparations.** Tablets (100 mg, 400 mg) for oral administration
Ethambutol Adverse Effects

- **Retrobulbar neuritis**: Decreased visual acuity or decreased red-green color discrimination that may affect one or both eyes.

- The effect is dose related, with minimal risk at a daily dose of 15 mg/kg. No difference was found in the prevalence of decreased visual acuity between regimens that contained EMB at 15 mg/kg and those not containing the drug.

- The risk of optic toxicity is higher at higher doses given daily (18% of patients receiving more than 30 mg/kg per day) and in patients with renal insufficiency.

- **Peripheral neuritis**: This is a rare adverse effect.

- **Cutaneous reactions**: Skin reactions requiring discontinuation of the drug occur in 0.2--0.7% of patients (68
Ethambutol

- Bacteriostatic / cidal
- Mechanism of Action
  - Interferes with RNA, protein synthesis
  - Requires growing organism
- Spectrum
  - M.TB., Non-tuberculous mycobacteria
**EMB**

- **Dose**
  - 15-25 mg/kg/day qd
  - 25-30 mg/kg/day tiw
  - 50 mg/kg/day biw
  - Max: 2.5 gm/day
    - (1600mg/qd, 2.4 gm tiw, 4 gm biw)

- **ADR**
  - Optic neuritis
  - Red/green discrimination
  - Acuity
    - Don’t exceed 50 mg/kg/day (18% > 50 mg/kg/d)
  - Increased uric acid levels
EMB

- Monitor
  - Vision
    - Color
    - Acuity
  - Renal function
  - Uric acid levels
Combination Products

- Rifamate
  - INH 150 mg + RIF 300 mg
  - Especially useful for extension phase of TX
  - Reduces chance of noncompliance
Treatment of Active Tuberculosis Part Two
“DOT Therapy Works!”

- 95% of patients with TB will be cured by DOT
  - Decreases morbidity and mortality and cost (~ $1500/pt)
  - Decreases spread of disease
    - Average patient with TB infects 30 other individuals
  - Decreases resistance
    - MDR costs ~ $250,000 to cure with only ~ 80% success
- 5% of patients with active TB will be unable to complete therapy; requiring legal interventions and facilities to cure them
  - In S.F. one non-compliant patient with MDR-TB was responsible for 40 other cases
Case Discussion: 2 year old close contact to a smear positive case
Second Line Drugs
Fluoroquinolones

- The fluoroquinolones target DNA gyrase and topoisomerase IV.
- These enzymes work by transiently breaking DNA and passing a region DNA through the break during DNA replication and transcription.
- The drugs form drug-enzyme complexes and block polymerase movement and hence inhibit cell growth.
Basic Structure of Quinolones
Rise of the Quinolones

- In 1985, Tsukamura reported that 19 patients with drug-resistant TB responded fairly well to therapy with what was then a novel fluoroquinolone, ofloxacin.
- Clinical experience soon followed, particularly in the New York MDR epidemic.
- No randomized trials of quinolones until more recently and there was no clear benefit over current regimens.
Quinolones Today

- However, a series of studies by Grosset and colleagues using a mouse model, has shown that after 28 days of treatment, moxifloxacin had a bactericidal activity comparable to that of isoniazid.
- Subsequent mouse studies showed that a regimen of rifampin, PZA, and moxifloxacin had a greater sterilizing effect than the usual four-drug regimen.
- In Dec 2005, Grosset has shown moxifloxacin may be a better companion drug for rifapentine than isoniazid in once weekly regimens.
Why Moxifloxacin?

- Excellent in vitro activity, including potent activity in a model of mycobacterial persistence
- Bactericidal and sterilizing activity in mice
- Favorable pharmacokinetic characteristics
- Good safety profile in post-marketing studies
- Interest by Bayer Pharmaceutical Company
Moxifloxacin and Rifapentine vs. Denver regimen in a Mouse Model

Proportion of mice with culture-positive lungs three months after completing treatment with four, five, and six months of the Denver regimen (rifampin plus isoniazid, 2/7) or once-weekly (1/7) rifapentine-based continuation regimens. Mice were considered to be culture positive if one or more colony-forming units was detected when the entire organ was plated.

*One of five lung homogenates harbored rifamycin-resistant mutants. Significant differences compared with the Denver regimen (rifampin plus isoniazid, 2/7) are shown as p = 0.04, p = 0.016. RH = rifampin plus isoniazid; MHP = moxifloxacin plus isoniazid plus rifapentine; HP = isoniazid plus rifapentine; P = rifapentine; MP = moxifloxacin plus rifapentine.
Moxifloxacin EBA Study

- 43 patients with newly diagnosed pulmonary TB randomized to isoniazid (300 mg), rifampin (600 mg), or moxifloxacin (400 mg)
- Quantitative sputum cultures before and during two days of treatment
- Log reduction in Colony forming units (CFU), day 0-2
  - Isoniazid: 0.77 (0.54 - 1.00)
  - Rifampin: 0.28 (0.15 - 0.41)
  - Moxifloxacin: 0.53 (0.28 - 0.71)

Gosling et al. Am J Respir Crit Care Med. 2003 Dec 1;168(11):1342-50
# Features of New Fluoroquinolones Relevant to TB Therapy

<table>
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<tr>
<th>DRUG</th>
<th>CMAX</th>
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<th>AUC</th>
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Long-term Tolerability of Moxifloxacin in TB Patients

- 20 patients for whom standard treatment not indicated
- Treated with 6HRM at usual doses
- Monthly laboratory monitoring
- 90% culture-negative at one month
- All completed treatment with no toxicity

Quinolones Summary

- Fluoroquinolones hold a great deal of promise in significantly reducing the “standard” treatment regimen by one third with perhaps greater efficacy.
- Animal studies and now later clinical trials support this possibility.
- Shorter treatment regimens may be a reality by decade’s end.
Linezolid

- Linezolid is an oxazolidinone antibiotic designed to treat Gram-positive bacterial infections.
- It also has considerable in vitro activity against MTB, with MIC(90) values on the order of 0.5 to 1.0 mcg/mL.
- These MIC values are similar to those reported with Gram-positive organisms.
- Linezolid has excellent oral bioavailability, producing serum concentrations on par with intravenous administration.
Linezolid

- Although linezolid generally is well tolerated in the short-term, long-term use, such as is required to treat TB, presents several challenges.
- Linezolid is known to be associated with myelosuppression when used for several weeks leading to anemia, leucopenia, pancytopenia, and thrombocytopenia.
- Anemia, peripheral neuropathy, and optic neuropathy have also been reported in small case series of TB patients receiving linezolid within multidrug regimens.
Capreomycin

- **Role in treatment.** Capreomycin is a second-line injectable.

- **Adults (maximum):** 15 mg/kg per day (1.0 g/day), usually given as a single daily dose five to seven times a week, and reduced to two or three times a week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

- **For persons greater than 59 years of age the dose should be reduced to 10 mg/kg per day (750 mg).** The dosing frequency should be reduced to 12–15 mg/kg two or three times per week in persons with renal insufficiency.

- **Children (maximum):** 15–30 mg/kg per day (1 g/day) as a single daily or twice weekly dose.
Capreomycin Adverse Effects

- **Nephrotoxicity:**
  - Nephrotoxic effects may result in reduced creatinine clearance or potassium and magnesium depletion.
  - Proteinuria is common.
  - Significant renal toxicity requiring discontinuation of the drug has been reported to occur in 20–25% of patients.

- **Ototoxicity:**
  - *Vestibular disturbances, tinnitus, and deafness appear to occur more often in elderly persons or those with preexisting renal impairment.*
Special Situations
Case Discussion:
38 year old man with HIV infection with TB and late CNS symptoms
TB Drugs and the CNS

- Before effective anti-tuberculosis chemotherapy, tuberculous meningitis was uniformly fatal.
- Tuberculous meningitis is associated with a high morbidity and mortality, despite prompt initiation of adequate chemotherapy.
- HIV-infected patients appear to be at increased risk for developing tuberculous meningitis.
- Patients presenting with more severe neurologic impairment such as drowsiness, obtundation, or coma have a greater risk of neurologic sequelae and a higher mortality.
TB Drugs and the CNS

- Chemotherapy should be initiated with INH, RIF, PZA, and EMB in an initial 2-month phase.
- INH and RIF, as well as the aminoglycosides, capreomycin, and the fluoroquinolones are available in parenteral forms for patients with altered mental status who may not be able to take oral medications.
TB Drugs and CNS Penetration

- INH  Excellent CNS penetration
- RIF  10-20% of serum concentration more with inflamed meninges
- RBN  Yes
- PZA  Yes Same as serum concentration
- EMB  Yes but it has no demonstrated efficacy
- SM   Minimal
- Cyclo Yes
- Ethion Yes
- Amik/Kan Minimal
- PAS  10-50% marginal
- FQ   ~20%
TB and the CNS

- On the basis of limited data, adjunctive corticosteroid therapy with dexamethasone is recommended for all patients, particularly those with a decreased level of consciousness, with tuberculous meningitis.

- The recommended regimen is dexamethasone in an initial dose of 8 mg/day for children weighing less than 25 kg and 12 mg/day for children weighing 25 kg or more and for adults.

- The initial dose is given for 3 weeks and then decreased gradually during the following 3 weeks.
Summary of TB Drug Actions

Christopher M Sassetti & Eric J Rubin
Shortening the Treatment Regimen
Shortening Treatment

- Rifampin, a member of the rifamycin group, is bactericidal against *M. tuberculosis* and other NTM.
- It is a semisynthetic compound derived from *Amycolatopsis rifamycinica.*
Shortening Treatment

- Rifampin acts on *M. tuberculosis* by inhibiting DNA-dependent RNA polymerase, blocking transcription.
- It is the most potent sterilizing agent in TB therapy
- Sterilizing activity is considered to be the feature most important to the length of the regimen.
- The greater the sterilizing activity, the shorter the regimen may be without substantial risk of relapse.
Higher Dose Rifampin

- Improved sterilizing activity and survival were achieved in the mouse and the guinea-pig with increased RIF doses.
- Studies by Verbist revealed dose-related killing of MTB in mice given RIF 5 to 40 mg/kg: a 2-log increase in killing occurred when the 5 mg/kg dose was doubled.
- There are similar RIF dose and concentration responses in humans.
- At the standard dose used in TB treatment, no plateau in activity is detected with RIF at 600 mg in vivo.
- This is in contrast to the standard dose of INH, at which the bactericidal activity of INH appears to plateau.
Higher Dose of Rifampin

- In a USPHS study, only 60% of those receiving 450 mg of RIF, while 75% of patients who had received 750 mg of RIF/day, had converted by 2 months.

- In an East African/British MRC trial using 450 mg of RIF in patients under 50 kg and 600 mg RIF in patients over 50 at months one and two, 29% and 73% of patients respectively had negative cultures.

- Compared to the 600 mg dose, the 1200 mg dose in humans appears to increase the frequency of culture conversion at both months 1 and 2, consistent with the mouse model results of Verbist and Nuermberger.
Toxicity of High Dose Rifampin

- The primary toxicities attributed to RIF, hepatotoxicity and flu-like syndrome, are not likely to occur more frequently with increased daily dosing.
- RIF hepatotoxicity appears to be idiosyncratic.
- Although there are some inconclusive reports of increased incidence of hepatotoxicity with RIF and INH used in combination, available data do not support an increase in hepatotoxicity in situations where higher doses of RIF are used.
- **At this time only use higher dose RIF with therapeutic drug monitoring.**
Rifapentine (RPNT)

- RPNT is the cyclopentyl derivative of rifampin, with the same mechanism of action and a similar overall toxicity profile.
- RPNT has a long plasma half-life (14–18 h compared to 2–3 h for RIF), although its $t^{1/2}$ is shorter than that of RBN.
- RPNT is more slowly absorbed than RIF or RBN.
- There is significant interest in identifying the dose, dosing frequency, and companion drugs to optimize the activity of RPNT.
- Also like RIF, RPNT-containing regimens that include MOXI and exclude INH appear to be more active in the mouse model.
Rifapentine and Shorter Regimens

- Although the approved dose of RPNT is 600 mg once weekly, planned and ongoing trials are examining higher doses or increased frequency of dosing.
- USPHS TB trial 29 will compare the antimicrobial activity and safety of a standard daily rifampin-based regimen to that of an experimental RPNT-based regimen.
- The Phase III RIFAQUIN study, which began enrolling patients in mid-2008, is designed to evaluate whether RPNT- and moxifloxacin-containing regimens can shorten treatment and reduce frequency of acquisition of rifamycin mono-resistance.
Quinolones and Shorter Regimens

- Recent studies have provided additional insight into the use of FQ for TB; the focus has been on regimen shortening with newer members of the class.
- First, in the mouse model, substituting MOXI for INH seems to enhance the regimen, leading to more rapid sterilization.
- Isoniazid has been described as antagonizing the sterilizing activity of the RIF-PZA combination in the mouse model.
- Mouse models have also demonstrated that escalation of rifamycin dose, in conjunction with moxifloxacin, can further accelerate sterilization.
Quinolones and Newer Regimens

- After the rifamycins, the fluoroquinolones (FQ) represent the next most potent class of drugs currently available to treat TB.
- Despite the potential of the FQ there are a number of concerns;
  - Rapid development of resistance
  - Resistance of other concurrent organisms such as Streptococcus
  - Adverse effects are not uncommon and may include prolongation of the QT interval, dysglycemia, and tendon rupture
New Drugs in Development
TMC207-Bedaquiline (Sirturo)

- The diarylquinoline R207910 (now known as TMC207) is distantly related chemically to the malaria drug chloroquine.
- The target of TMC207 is the proton pump of adenosine triphosphate (ATP) synthase.
- It is equally active against drug-sensitive and drug-resistant strains of MTB; it is also active against many other types of mycobacteria.
PA-824

- PA-824 is a nitroimidazopyran, a chemical cousin of metronidazole, and it is being advanced through clinical development by the Global Alliance for TB Drug Development.
- Like metronidazole, it is proposed that PA-824 is a prodrug, which is activated inside of mycobacteria, resulting in the disruption of mycolic acid synthesis and protein synthesis in a dose-dependent manner.
- In the mouse model a range of activity has been shown and the best dose and combination is still being assessed.