MANAGEMENT OF TUBERCULOSIS

Dean B. Ellithorpe, M.D.
Clinical Professor of Medicine
Section of Pulmonary Diseases, Critical Care and Environmental Medicine
Tulane University School of Medicine
INTRODUCTION
Underlying principles for successful treatment of tuberculosis

- Multi-drug regimen with two or more drugs to which TB bacillus is susceptible
- Drugs given in adequate doses
- Drugs taken regularly
- Drugs taken for sufficient period of time
- Rifamycins mainstay of current anti-TB Rx
- PZA necessary for 6 month regimens
ATS CDC IDSA 2003 Statement on Treatment of Tuberculosis

- TB treatment regimens outlined in this presentation are based on the 2003 ATS/CDC/IDSA joint Statement: Treatment of Tuberculosis
- There are 4 rifamycin based regimens recommended for drug susceptible M. tb
- Treatment regimens consist of an Initial Phase (IP) of 8 weeks and a Continuation Phase (CP) of a minimum of 4 months
- An extended Continuation Phase of 7 months is required for patients with cavitary PTB with positive AFB culture @ 2 months of therapy, or if the IP did not include PZA)
Treatment Regimens

- Preferred IP consists of RIF, INH, PZA, & EMB RIPE (HRZE)
- CP for patients infected with susceptible TB consists of RIF & INH
- Minimum total duration of therapy is 6 months
- An extended CP of 7 months for a total duration of 9 months appropriate in certain circumstances (very extensive disease with high bacterial burden)
Specific Regimens

- Regimens 1/1a, 1/1b, and 2/2a commonly used
- Regimens 1/1c and 2/2b with CP of once weekly Rifapentine are not used in the U.S.
- Regimen 3 with three time a week dosing is generally not used in the United States
- Regimen 4 does not include PZA
- EMB included in IP when the incidence of primary INH resistance exceeds 4% (LA)
- All regimens are based on likely susceptibility of TB bacillus to rifampin
Details of Specific Regimens

- Regimen 1 IP - Daily RIPE for 8 weeks
- followed by either
- Regimen 1a CP - Daily RIF & INH for 4 months (18 weeks)
- or
- Regimen 1b CP - Twice weekly INH and RIF for 4 months (18 weeks)
Details of Specific Regimens (continued)

- Regimen 2/2a IP - Daily RIPE for 2 weeks and then twice weekly RIPE for 6 weeks
- followed by
- Regimen 2a CP - Twice weekly RIF and INH for 4 months (18 weeks)
- Regimen 2/2a, with mostly twice weekly dosing, facilitates DOT and is utilized by many city/state TB Programs (LA OPH) - This is default regimen for DOT
Details of Specific Regimens (continued)

- The above Regimens all begin with daily RIPE for at least 14 days (2 - 8 weeks)
- The minimum duration of Rx is 6 months
- Total doses received is more important than the weeks or months of therapy
- Extended CP of 7 months for patients with cavitary PTB and positive AFB cultures at two months of therapy.
Details of Specific Regimens (continued)

- Regimen 4 IP - Daily RIF, INH & EMB for 8 weeks followed by
- Regimen 4a CP - Daily RIF & INH for 7 months or
- Regimen 4b CP - Twice weekly RIF & INH for 7 months
- Regimen 4 does not include PZA and it is not acceptable for a 6 month short course of treatment.
- This Regimen only utilized when PZA cannot be used
Extensive Pulmonary Tuberculosis

• Extensive/ “far advanced” pulmonary TB is bilateral, multilobar, cavitary disease
• Smear positive, cavitary disease = high bacterial burden
• For select cases may consider more extensive Rx:
• Regimen 1 IP of all daily RIPE for 8 weeks
• followed by
• Regimen 1a CP - Daily RIF & INH for 4 months
• or
• Regimen 1b CP - Twice weekly RIF & INH for 4 months
• Extended 7 months CP of therapy may also be appropriate
• Clinical judgment by a TB expert!
Drugs and Doses

• Doses are modified based on lean body weight. INH and rifampin doses do not need to be weight adjusted for adult patients except those weighing <40 Kg (90 lbs).
• Doses for EMB and PZA are always weight based.
• Doses for all injectable agents and most other second-line drugs are weight based.
• PZA and EMB doses can be based on weight ranges: 40-55 Kg, 56-75 Kg and 76-90 Kg.
Drug Cautions

- PZA is relatively contraindicated in patients with symptomatic gout.
- PZA increases uric acid and interferes with allopurinol.
- For patients with CrCl <30 ml/min modify PZA dose schedule to thrice weekly.
- Exercise caution with EMB in over 65 years of age or patients with impaired vision.
- For patients with CrCl <30 ml/min modify EMB dose schedule to thrice weekly.
Standard Drug Doses

• RIF: 600 mg daily or twice weekly
• INH: 300 mg daily; 900 mg twice weekly
• PZA: 1000 mg (40-55 Kg), 1500 mg (56-75 Kg), or 2000 mg (76-90 Kg) daily; 2000 mg, 3000 mg, or 4000 mg twice weekly
• EMB: 800 mg (40-55 Kg), 1200 mg (56-75 Kg), or 1600 mg (76-90 Kg) daily; 2000 mg, 2800 mg or 4000 mg twice weekly
DOT - Directly Observed Therapy

- DOT is the Standard of Care for patients with pulmonary tuberculosis (PTB) in the United States.
- Metropolitan New Orleans DOT programs are the responsibility of the Disease Intervention Specialists (DIS) for the Metro Region 1 at the Louisiana Office of Public Health (OPH).
- DOT is administered either daily (5 or 7 days a week) or twice weekly and may be accomplished by several different schemes – field DOT, clinic DOT, or DOT by proxy.
- The LA TB Control Program gives priority for DOT to AFB-smear positive PTB patients and to HIV-coinfected TB patients.
Common Adverse Effects

- GI upsets
- Skin rashes and pruritus
- Drug fever
- CNS complaints
- Arthralgias
- Paresthesias
- Red-orange discoloration of body fluids - Warn the patient!
Drug-Drug Interactions

• HAART
• Rifampin - Induces cytochrome P450 (BCP, Wafarin, Methadone, Benzos)
• Isoniazid – Inhibits cytochrome P450 (Phenytoin, Carbamazepine, Diazepam)
Drug Induced Liver Injury - DILI

- DILI caused by INH, PZA and rifamycins
- Most DILI is caused by INH or PZA.
- Hepatotoxicity defined by elevated ALT >3x ULN with symptoms or ALT >5x ULN without symptoms.
- Abnormal baseline ALT/AST is independent risk factor for DILI.
- Increasing age (>35 years old) is associated with an increasing incidence of hepatotoxicity due to INH.
- Modest transient increase in ALT/AST (<3x ULN) may occur in 10-20% of patients treated with the standard four-drug regimen.
- This typically occurs during the first two to three months and generally resolves by the 3rd month of therapy. These patients are asymptomatic.
“Culture negative” PTB

- “Culture negative” PTB - clinical PTB with negative AFB cultures
- May be considered for an abbreviated 4 month period of treatment of
- Regimen 2 IP - RIPE for 8 weeks followed by
- Regimen 2a CP - RIF and INH for additional 2 months
- Therapy may be administered twice weekly after the initial 2 weeks of daily therapy (DOT) or
- Daily therapy if self administered
- Do not use this 4 month regimen for HIV-coinfected patients
- This regimen is not intended for culture negative EPTB
Special Situations

**Extrapulmonary TB (EPTB)** - All standard treatment Regimens are appropriate for treatment of EPTB

- Bone and CNS tuberculosis should receive a minimum of 9 to 12 months of therapy
- An abbreviated 4 month regimen is not intended for culture negative extra-pulmonary TB (EPTB)
- EPTB cases frequently have negative AFB cultures

**TB during pregnancy** - Treatment is 9 month Regimen 4/4b with an IP of daily RIF, INH and EMB for 8 weeks followed by CP of twice weekly RIF and INH for 7 months
- INH, RIF and PZA are FDA Category C. EMB is FDA Category B
- PZA is generally not recommended during pregnancy In the U.S.
- Injectable agents are not recommended during pregnancy
HIV-Coinfected Patients

- Standard six month treatment regimens are acceptable for most HIV-infected patients with TB.
- For HIV-coinfected patients with CD4+ cell counts <100 cells/μl, recommended regimen is all daily 6 month Regimen 1/1a: IP of daily RIPE for 8 weeks followed by CP of daily RIF and INH for 4 months.
- Daily therapy may also be preferable for all HIV-infected patients with extensive PTB.
- For HIV-coinfected patients receiving HAART, Rifabutin may have to be substituted for Rifampin.
- Coordinate Rx with HIV Physicians.
- A recent study from San Francisco suggests a decreased risk of relapse in HIV-coinfected patients who receive all daily therapy and are treated for longer than 6 months.
TB and Liver Disease

- Patients with advanced liver disease may require a regimen with only one or no hepatotoxic drug
- RIF should be retained if possible
- EMB, which is non-hepatotoxic, is generally always included
- Additional agents may include Moxifloxacin, Cycloserine, and an IA
- The duration of treatment with such regimens should be 12–18 months
- For severe liver disease requiring a total non-hepatotoxic regimen a four drug program of EMB, Moxifloxacin, Cycloserine and an IA may be used
- The duration of treatment with this regimen should be 18-24 months
- Monitor with monthly LFTs (AST, ALT and Bilirubin).
- Conventional treatment regimens generally can be used safely in patients with Hepatitis C and modest AST/ALT elevations
Drug Resistance and Intolerance

- **INH resistance or intolerance** -
  RIF, PZA and EMB **daily** for 6-9 months
  RIF & EMB for 12 months (If cannot tolerate PZA >2 months)
- **RIF resistance** -
  INH, EMB, and moxifloxacin **daily** for 12-18 months supplemented with PZA for the first 2 months of therapy. An injectable agent may be included for 2-3 months for extensive disease or to shorten therapy to 12 months
- **RIF intolerance** –
  INH, PZA and EMB with or without moxifloxacin for 9-12 months or 18 months of INH and EMB
- **PZA cannot be used** –
  Daily INH, RIF, and EMB for 8 weeks and a CP of either daily or twice weekly INH and RIF for 7 months
- **Moxifloxacin is promising** - A recent Johns Hopkins study reported significantly better culture conversion at 2 months with regimen containing moxifloxacin instead of EMB (85% vs. 68%).
SPUTUM CONVERSION and INFECTIVITY

- Positive AFB smears, cavitary lung disease, not on therapy or just started therapy are infectious
- Clinically improving, 3 consecutive negative AFB smears, and received a minimum of 2-3 weeks of anti-TB Rx are “relatively” noninfectious
- Drug resistant cases of TB should be considered infectious until AFB-culture negative
- 80% of cases due to susceptible TB become culture negative within two months of therapy
- Mean time for conversion to a negative smear is 33 to 38 days.
- Mean time for conversion to negative culture is 32 to 34 days
MANAGEMENT OF TUBERCULOSIS

• THE END

• QUESTIONS?

• “Tulane Guidelines for Management of Tuberculosis in Adults”