TUBERCULOSIS TREATMENT: MEDICATIONS & REGIMENS

TREATMENT: GENERAL PRINCIPLES
• ALWAYS USE AT LEAST 2 DRUGS:
  – Begin with 4 pending sensitivities
  – Natural incidence of spontaneous resistance to any 1 drug= 1 in 10,000 organisms
  – Bacilli resistant to 1 will be killed by others
  – Natural resistance to 2 drugs spontaneously= 1 in $10^{10}$
• Prolonged Length of Rx: 6-9 months DEPENDING UPON REGIMEN
• Directly Observed Therapy: ALL SHOULD BE

ISONIAZID (INH) Isonicotinyl Hydrazine or isonicotinic acid hydrazide
• INH available as 100 mg and 300 mg tablets for oral administration
• INH empirical formula: C$_6$H$_7$N$_3$O
• MOLECULAR WEIGHT: 137.14.

MECHANISM OF ACTION
• INH INHIBITS SYNTHESIS OF MYCOLIC ACIDS
• MYCOLIC ACID IS ESSENTIAL COMPONENT OF BACTERIAL CELL WALL
• INH IS BACTEROICIDAL AGAINST ACTIVELY GROWING INTRACELLULAR & EXTRACELLULAR ORGANISMS
• INH RESISTANT M. tuberculosis organisms develop rapidly when INH monotherapy administered

Treatment:
First Line Drugs
1. ISONIAZID = INH
• Bacteriocidal against dividing organisms
• Dose = 300mg = one pill = well absorbed
• Good CNS penetration
• Can be used during pregnancy
CLINICAL PHARMACOLOGY

- Peak blood levels within 1 - 2 hrs after oral administration
- Peak blood levels decline to 50% within 6 hours; 50-70% of dose excreted in urine in 24 hours
- Diffuses readily into all body fluids, tissues, organs, and excreta (saliva, sputum, and feces)
- Passes through placenta & into breast milk in concentrations comparable to those in plasma

INH TOXICITY: HEPATIC

Chemical vs. Clinical Hepatitis

20% patients have rise in transaminases; resolves without stopping INH; usually occurs within first 1-3 months of RX.
- Rise in transaminase >5 times normal is significant and INH should be stopped
- Toxicity is age related: <35 = 0.3%; >65 = 4%

INH TOXICITY: NEUROPATHY

Uncommon; dose-related

Occurs most often in malnourished & those predisposed to neuropathy (alcoholics, diabetics)

Usually preceded by paresthesias of feet & hands

Pyridoxine indicated for patients with conditions where peripheral neuropathy common: diabetes, uremia, alcoholism, AIDS

Pyridoxine indicated for pregnant women on INH

2. RIFAMPIN (RMP):

Enables short course treatment

- Bacteriocidal
- Dose = 600mg = (2) 300mg capsules = well absorbed
- Good CNS penetration if meninges inflamed
- Can be used in pregnancy

RMP: MECHANISM OF ACTION

- Inhibits DNA-dependent RNA polymerase in susceptible strains of bacteria
- Absorption: Almost completely absorbed

ENABLES SHORT COURSE TREATMENT:

6-9 months vs. 18-24 months w/out RMP
CLINICAL PHARMACOLOGY

- **C max** is 1 to 4 hr (oral)
- Absorption decreased 30% if taken w/food
- Distribution: Diffuses well into most body tissues and fluids, including CSF
- Crosses placenta & distributes into breast milk
- Protein binding is 89%

RIFAMPIN TOXICITY

- Most common adverse reaction = GI upset
- Can cause cholestatic jaundice
- Skin rash
- Thrombocytopenia (rare)
- Bonded to inactive dye which is excreted in urine, sweat, tears: Colors these fluids orange
- **MAJOR PROBLEM WITH RMP IS DRUG-DRUG INTERACTION**

**Rifampin**

- Induces hepatic microsomal enzymes: P450 system; accelerates metabolism of many drugs making them less effective or ineffective when rifampin is being given:
  - Methadone
  - Coumadin
  - Estrogen: Oral Contraceptives
  - Glucocorticoids
  - Digitoxin
  - Anti-arrhythmic agents (quinidine, verapamil, mexiletene)
  - Theophylline
  - Anti-convulsants
  - cyclosporin

**PROTEASE INHIBITORS**
3. PYRAZINAMIDE (PZA)

- Bactericidal in acid environment (macrophages)
- Dose = weight dependent = 25-30 mg/kg: PATIENT MUST BE WEIGHED
- Main role in sensitive disease is to reduce length of treatment from 9 months to 6 months
- Do not use in pregnancy: no teratogenicity data

CLINICAL PHARMACOLOGY

- Well absorbed from GI tract
- Peak plasma concentrations in 2 hours
- Widely distributed in body tissues including lungs, liver and CSF when meninges inflamed
- 10% bound to protein
- Half-life (t½) = 9-10 hours in patients with normal renal function but may be prolonged in pts with renal insufficiency
- 70% of oral dose excreted in urine within 24 hours, mainly by GFR

PZA structural formula:
C₅H₅N₃O  M.W.123.11

PYRAZINAMIDE TOXICITY:

- HYPERURICEMIA:
  - PZA inhibits renal excretion of urates
  - All patients have increase in uric acid levels: usually entirely asymptomatic
  - Occasionally causes arthralgias: Offer patient choice of NSAIDS or D/C PZA and treat longer
  - Rarely causes acute gouty arthritis, most often in elderly: STOP PZA
- HEPATIC:
  - Increase in transaminases
  - Chemically similar to isoniazid

MECHANISM OF ACTION
UNKNOWN

- PZA MAY BE BACTERIOSTATIC OR BACTERICIDAL AGAINST M. tuberculosis DEPENDING ON CONCENTRATION OF DRUG ATTAINED AT SITE OF INFECTION
- IN VITRO & IN VIVO DRUG IS ACTIVE ONLY AT SLIGHTLY ACIDIC pH

4. ETHAMBUTOL (EMB)

- Most important function is prevention of resistance
- Used in drug resistance and when INH or RMP cannot be used (INH hepatotoxicity or RMP drug-drug interactions)
- Bacteriostatic
- Can use in pregnancy
- Primarily excreted by kidney so must adjust dose in renal insufficiency
ETHAMBUTOL

- Dose = weight dependent = 15-25 mg/kg: WEIGH PATIENT
- Toxicity more likely with higher dose
- Poor CNS penetration
- Can use in pregnancy

CLINICAL PHARMACOLOGY

- EMB at 25 mg/kg attains peak serum levels 2 to 4 hours after administration
- Following oral administration of EMB approximately 50 percent of initial dose excreted unchanged in the urine w/in 24 hours
- No drug accumulation observed w/ consecutive single daily doses of 25 mg/kg in patients with normal kidney function
- BUT marked accumulation in patients with renal insufficiency: TOXICITY

ETHAMBUTOL TOXICITY = RETROBULBAR NEURITIS

- Blurred vision = initial symptom
- Red-green color blindness common and may be picked up earlier with testing
- Dose related: <1% of those receiving 15 mg/kg; recommended dose is 15-25 mg/kg
- CHECK VISUAL ACUITY & COLOR VISION AT BASELINE AND MONTHLY: ISHIHARA

TREATMENT REGIMENS: ALL SHOULD BE DOT

IMMUNOCOMPETENT & DRUG SENSITIVE

- 6 Months total: FIRST 2 MONTHS = INITIATION OR INTENSIVE PHASE
  -2 months H/R/Z/E + 4 months H/R daily for entire 6 months
  -2 months H/R/Z/E daily + 4 months H/R BIW
  -TIW for entire 6 months: 2 months H/R/Z/E + 4 months H/R

- 9 Months total: 9 months H/R without PZA: Pregnant women, Elderly if PZA intolerant, & M.bovis (PZA resistant)
- Drop EMB when sensitivities known

EXTEND CONTINUATION PHASE 3 MONTHS IF:

- CAVITARY DISEASE & POSITIVE SPUTUM CULTURE AFTER 2 MONTHS INITIAL PHASE
- ASSOCIATED WITH INCREASED RELAPSE IN CLINICAL TRIALS
- EXTENDED CONTINUATION PHASE DECREASED RELAPSE IN SILICOTUBERCULOSIS FROM 20% TO 3%
- HIV INFECTED PATIENT WITH SPUTUM CULTURE STILL POSITIVE AT 2 MONTHS

MDRTB: DEFINITION = Resistance to Both INH & RMP

- CANNOT TREAT WITH EITHER INH OR RMP
- NEED 6-9 Month of injectable + 3 oral agents to which organism sensitive for total 24 months treatment after culture conversion
- Second line drugs necessary
- Poor prognosis: >50% treatment failure
- Old data published from National Jewish Center in Denver; referral center for secondary drug resistance
SECOND LINE DRUGS

- **INJECTABLES:**
  - STREPTOMYCIN
  - AMIKACIN
  - KANAMYCIN
  - CAPREOMYCIN

- **ORAL AGENTS:**
  - QUINOLONES: LEVOFLOXACIN OR MOXIFLOXACIN
  - CYCLOSERINE
  - ETHIONAMIDE
  - P-aminosalicylic acid (PAS)

INCREASING TOXICITY & SIDE EFFECTS

- **ORAL AGENTS:**
  - CYCLOSERINE: narrow therapeutic-toxic window
  - CNS TOXICITY: CONVULSIONS & PSYCHOTIC DEPRESSION which can lead to suicidal behavior
  - ETHIONAMIDE: SEVERE GI TOLERANCE (VOMITING);
  - HEPATOTOXICITY similar to INH

INJECTABLES

- **AMIKACIN: NEPHROTOXIC**
- **STREPTOMYCIN: NEUROTOXIC TO VIII NERVE**
  - Both auditory and vestibular ototoxicity
  - Partial or total irreversible deafness may continue to develop after drug is stopped
  - Other features of neurotoxicity include paresthesia, twitching, and seizures.
  - Teratogenic: Contraindicated during pregnancy
- **KANAMYCIN: SIMILAR TO STREPTOMYCIN**
- **CAPREOMYCIN**
**XDR TUBERCULOSIS: DEFINITION**

- RESISTANT TO INH & RMP
- RESISTANT TO FLUOROQUINOLONES
- RESISTANT TO 1 OF THE INJECTABLE DRUGS: AMIKACIN, KANAMYCIN OR CAPREOMYCIN

---

**Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa**

Summary: The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

Methods: We conducted enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

Results: From January 2005 to March 2008, sputum was obtained from 1539 patients. We diagnosed MDR tuberculosis in 325 patients, of whom 53 had XDR tuberculosis. Prevalence among HIV-positive patients who were culture-positive for tuberculosis was 39% (IPT patients) and 4% (NC) for XDR tuberculosis. Only 55% (30 of 47) of patients with XDR tuberculosis had never been previously treated for tuberculosis. 47% (20 of 42) had a previous hospital admission. 42 patients with XDR tuberculosis who were tested for HIV were re-infected. 12 of 35 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis (IQR 1-41) among the 42 patients with confirmed HIV death. Among patients who died, 42% had a previous hospital admission. 42% of patients died in the year after diagnosis. Further studies are needed to determine the effectiveness of antiretroviral therapy on delaying tuberculosis death.