

Lecture 15:Antituberculosis Drugs

Dolly Mehta, Ph.D.

Knowledge Objectives

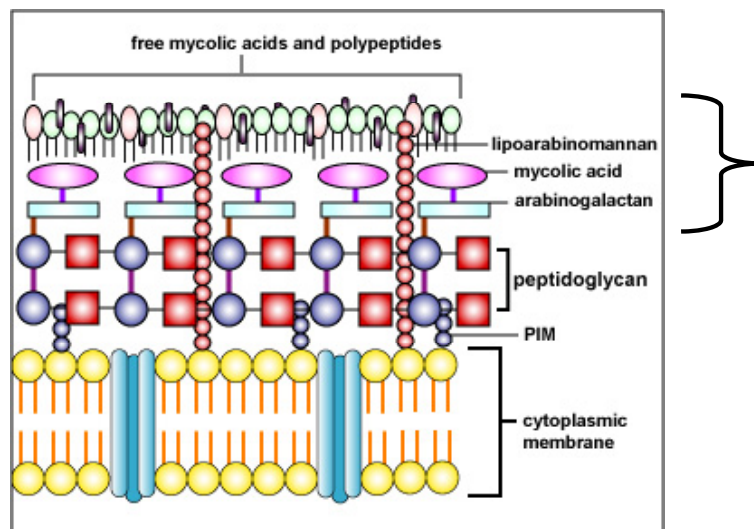
- 1 .Know the major symptoms of tuberculosis and leprosy.
2. Know the mechanisms of action of first and second line of anti-TB drugs.
3. Know the antimycobacterial agents used in prophylaxis and treatment of TB.
4. Know the most common adverse effects of the therapy.

Drug List

isoniazid
pyrazinamide
rifampin
ethionamide
ethambutol
aminosalicylic acid (PAS)
streptomycin
cycloserine

Anti-tubercular agents and Anti-leprosy

Mycobacterium tuberculosis



Characteristics of *Mycobacterium tuberculosis*

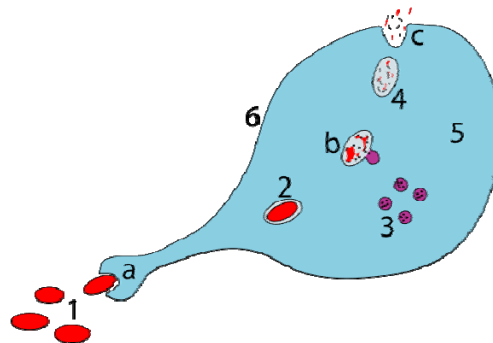
Slow cell division

Can withstand weak disinfectants

Survive in a dry state for weeks

Unique cell wall provide resistance and is a key virulence factor

Lung alveolar macrophage



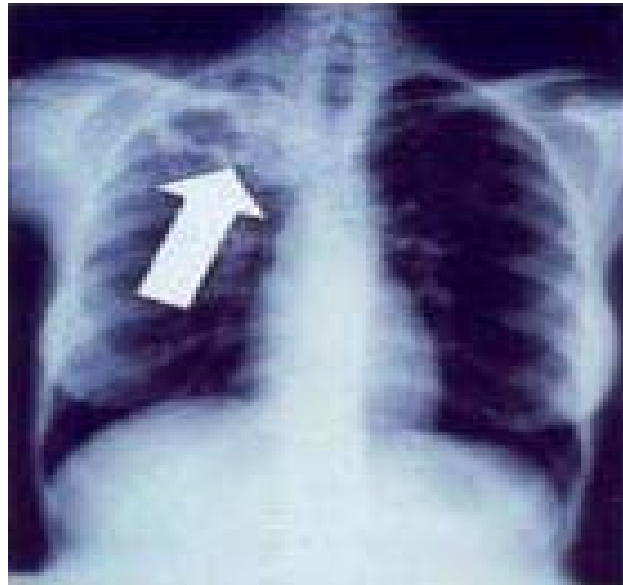
1. Pathogens
2. Phagosome
3. Lysosomes
4. Waste material
5. Cytoplasm
6. Cell membrane

***M. Tuberculosis* cell-wall** prevent the fusion of the phagosome with a lysosome.

UreC gene, which prevents acidification of the phagosome;

bacteria can neutralize reactive nitrogen intermediates.

- lungs (Pulmonary TB) primary
- lymph nodes (tuberculous adenitis or scrofula)
- Brain and CNS (Meningeal TB)
- skin and the bones
- Liver
- kidney.



Tuberculosis Chest X-ray with TB cavity right upper lobe

REMERGING as a plague globally

2002-2010----- 1 billion persons will be
newly colonized

Reasons

Mycobacteria

grow slowly and live **dormantly**

agile in developing resistance

many antibiotics cannot penetrate the cell wall

- Patient compliance
- drug toxicity
- drug interactions (HIV and TB)

Treatment

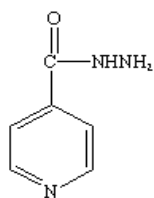
Atleast **2 different drugs** to which organism is susceptible

Treat for sufficient duration to prevent relapse

↙ First line
↘ Second line

Isoniazid (INH, Niconyl, Hyzyd) Rifampin (Rifadin, Rimactane)* Ethambutol (Myambutol) or Streptomycin Pyrazinamide	} First Line
Moxifloxacin (gatifloxacin) Cycloserine Capreromycin Ethionamide (Trecator-sc) Aminosalicic acid (PAS) (Panasol) Amikacin Kanamycin linezolid	} Second Line

Isoniazid (INH)



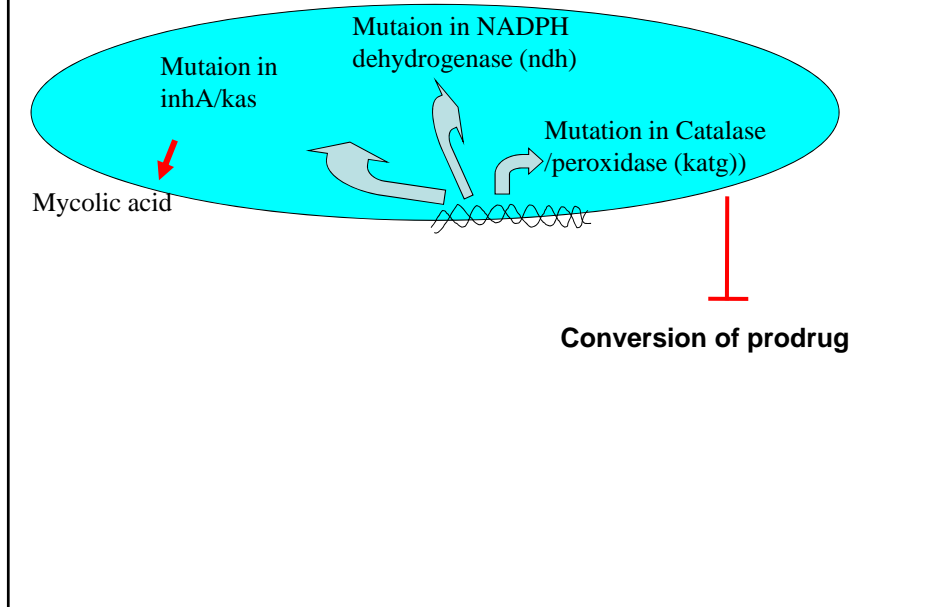
Bacteriostatic---resting mycobac
Bactericidal---growing mycobact

prodrug $\xrightarrow{\text{catalase-peroxidase}}$?? Active drug

I. Mechanism of action

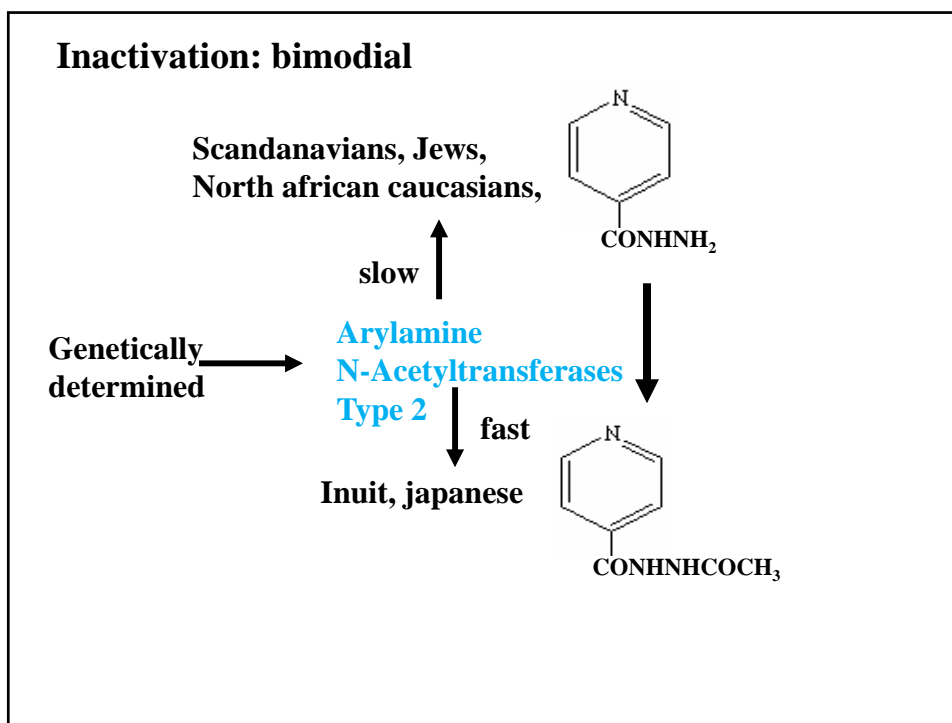
Inhibits synthesis of **mycolic acids**

Mechanism of Resistance



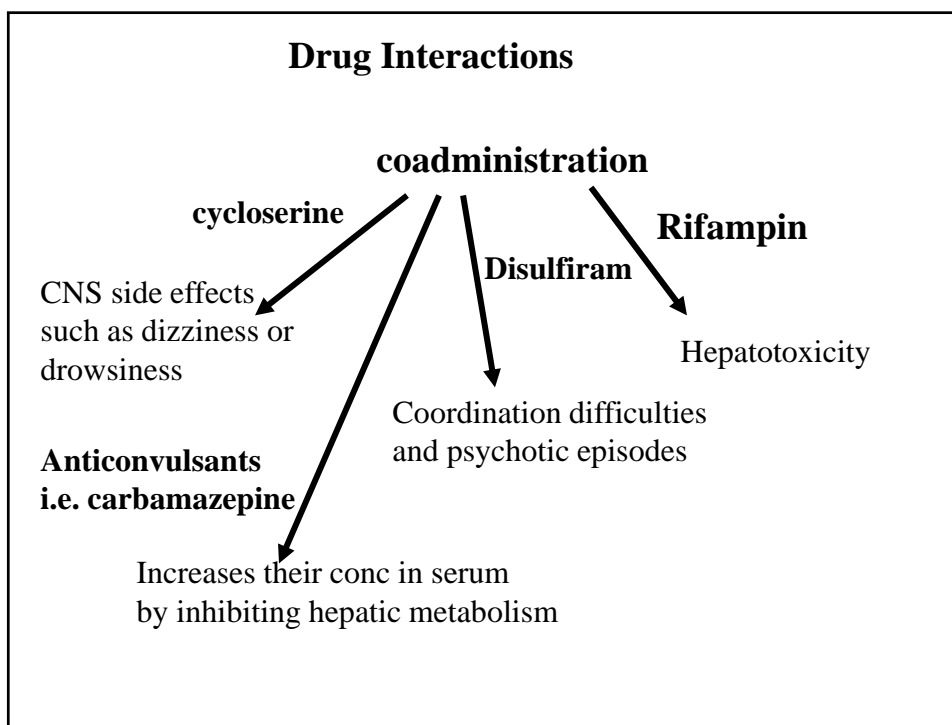
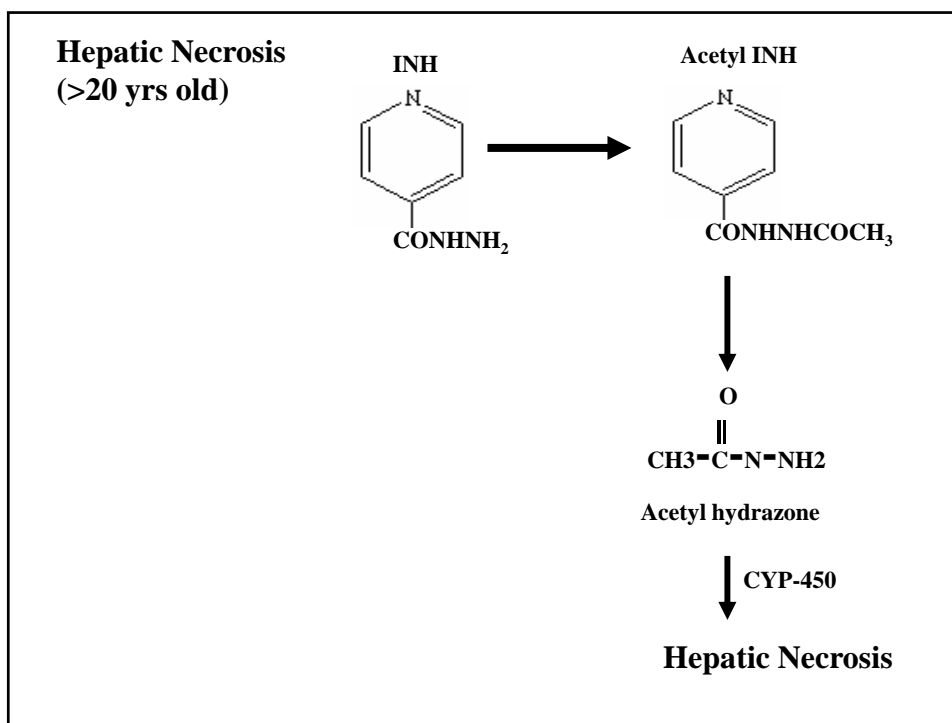
Absorption, Distribution, and Excretion

- Well-absorbed by GI tract
- Diffuses all body fluids including CSF;
(inflamed meninges conc in tissue = plasma)
- Al^+ -antacids interfere with absorption
- 75-95% Eliminated as acetylated by products via renal system
(24 hrs)



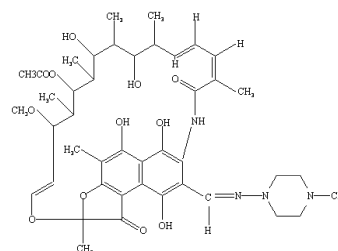
Untoward Effects

- Hypersensitivity: fever, various skin eruptions, etc
- Hematological reacns: eosinophilia, thrombocytopenia etc
- Arthritic symptoms
- pyridoxine deficiency (competes with vit B6)



Rifamycins (RIF) (bactericidal)

(rifampin, rifabutin, rifapentine)
Complex macrocyclic antibiotics

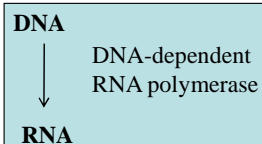


Mechanism of action

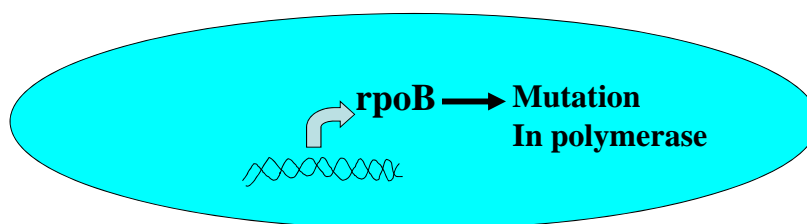
forms complex with β -subunit of
DNA-dependent RNA polymerase



Blocks initiation of chain
formation in RNA synthesis



Mechanism of Resistance



Absorption, Distribution, and Excretion

- absorbed by GI tract; aminosalicylic acid decreases the absorption

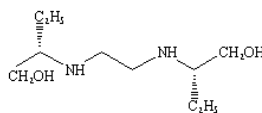
Deacetylated via enterohepatic circulation after which it is eliminated by bile.

- Diffuses all body fluids including CSF;

Untoward Effects

- Generally well-tolerated
- Induces hepatitis in patients with:
chronic liver disease, alcoholic or older patients
- Flulike symptoms
- By inducing **CYP1A2, 2C9** → **decrease half life** of
HIV protease inhibitors
digitoxin, verapamil etc

**Rifapentine half life > rifampin, rifabutin;
rifabutin preferred in HIV-infected patients**

Ethambutol (Myambutol)**•Synthesis of outer coating of cell wall**

inhibits **arabinosyltransferase** and thereby prevent conversion of D-arabinose into arabinogalactan required for synthesis

Resistance: single amino acid mutation in the embA gene

Absorption, Distribution, and Excretion

- Well-absorbed
- Less-toxic so replaced Aminosalicylic acid
- Effective when given with INH
- Excreted by tubular secretion in addition to glomerular secretion

Untoward Effects

Optic neuritis

visual acuity red:green; reversible

Streptomycin

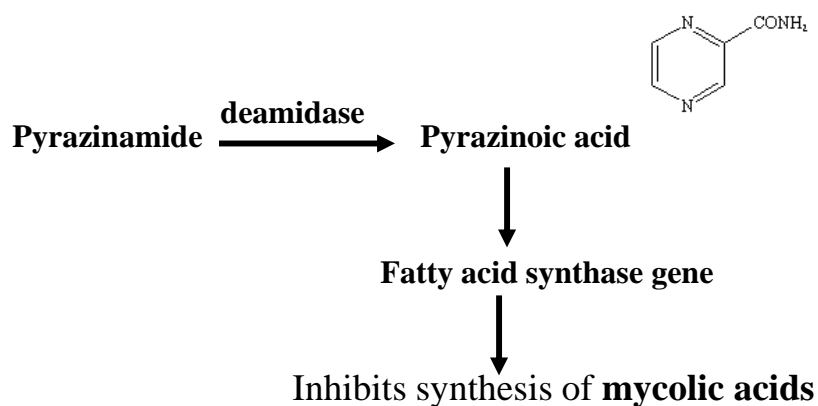
Very potent against mycobacteria

Recommended when less potentially hazardous therapeutic agents are ineffective or contraindicated

OR

Added in patients with serious forms of TB
i.e. **Disseminated meningitis**

Pyrazinamide (Important for short term TB treatment)



Absorption, Distribution, and Excretion

- Well-absorbed from GI
- Diffuses all body fluids including CSF
- Eliminated via glomerular filtration (half life > in older)

Untoward Effects

Liver injury, inhibits **urate excretion, gout**
anorexia, vomiting etc
(NOT recommended in pregnant woman in US)

Quinolones

Gatifloxacin (Tequin) }
Moxifloxacin (Avelox) } **For multidrug-resistant TB**

Inhibits DNA gyrase and topoisomerase

Aminosalicic acid (similar to sulphonamides)

Linezoid (ZYVOX)**Mechanism of action:**

binds P site of 50S and inhibits protein synthesis

Untoward Effects

- Myelosuppression including anemia, leukopenia, thrombocytopenia,
- Palpitation in patients on adrenergic or serotonergic drugs
- Peripheral and optic neuropathy

Ethionamide (Trecator-sc)

NADPH-specific FAD monooxygenase
 prodrug $\xrightarrow{\hspace{1.5cm}}$ Active drug

Mechanism of action

↓
**Fatty acid
 synthase gene**
 ↓
**Inhibits synthesis of
 mycolic acids**

Absorption, Distribution, and Excretion

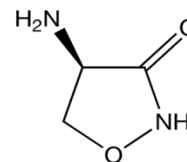
- Slowly absorbed
- Diffuses all body fluids including CSF
- Eliminated via hepatic sys
- **Secondary agent when primary agents fails**

Untoward Effects

- Anorexia, nausea, vomiting
- Postural hypotension, depression, drowsiness common
- Blurred vision, headache; **VitB6 relieves neurological sym**

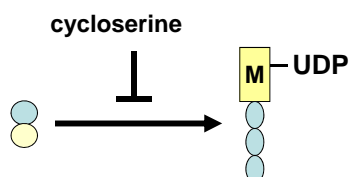
Cycloserine (Seromycin) D-4-amino-3-isoxazolidone

structural analog of D-Ala (acts as a competitive inhibitor)



stable in alkaline solution;
destroyed rapidly in neutral or acid pH

Mechanism:



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Absorption, Distribution and Excretion

70-90% Orally absorbed;

**distributed throughout body fluids
(concentration in CSF= plasma)**

Slowly metabolised; 50% excreted UNCHANGED in urine in 1st 12 hrs

renal patients: accumulate to toxic conc, removed by dialysis

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Untoward Effects

**CNS: headache, tremor, confusion etc
(symptoms disappear after drug is withdrawn)
Large dose or concomitant use of alcohol → seizures**

CONTRAINDICATED: Epileptic patients

Caution: patients with history of depression or suicidal attempts

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Immunomodulators

Interferon- γ (Actimmune)

Activates macrophages to kill *M. tuberculosis*

Aerosolised delivery in lungs of multidrug-resistant TB patients; enhances local immune stimulation

Chemotherapy of tuberculosis

6 month protocol

2 months: IRPE (isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin)

4 additional months: IR (isoniazid; rifampin)

HIV patients: may benefit from longer treatment 9-12 months

Chemoprophylaxis of tuberculosis

To treat latent infection

Identified by + delayed-type hypersensitivity reaction
to a purified protein derivative (Tuberculin test)

**Classical: 9 months of isoniazid or 4 months
rifampin (if isoniazid cannot be used)**

XDR: extensively drug resistant TB

Comprehensive Treatment of Extensively Drug-Resistant
Tuberculosis. [Carole D. Mitnick...](#) [Mercedes C. Becerra](#). NEJM : August
7, 2008 vol. 359 no. 6

XDR { *Mycobacterium tuberculosis* strains with resistance to at least isoniazid,
rifampin, and members of three of six classes of second-line drugs

Of the 651 patients tested, 48 (7.4%) had extensively drug-resistant tuberculosis; the
remaining 603 patients had multidrug-resistant tuberculosis.

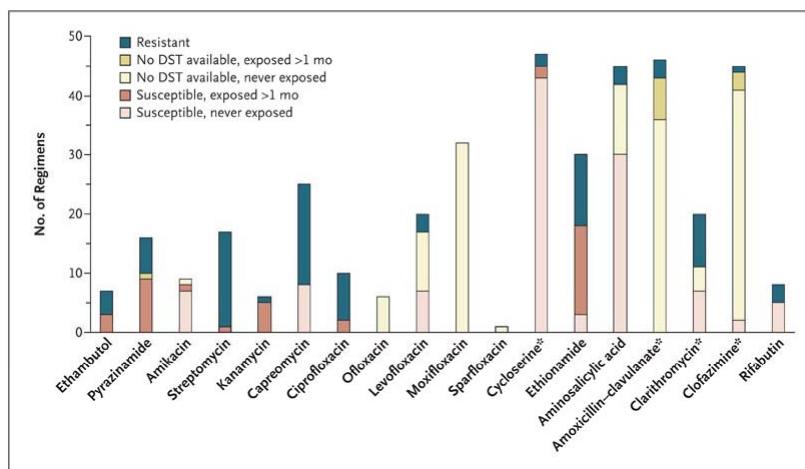


Table 4. Response and Time to Response According to Type of Resistance at Beginning of Individualized Treatment Regimen.

Outcome	XDR Tuberculosis (N=48)	MDR Tuberculosis (N=603)	Effect Estimate and P Value*
Response at end of treatment			
Good outcome — no. (%)	29 (60.4)	400 (66.3)	
Cured	29 (60.4)	395 (65.6)	
Completed†	0 (0.0)	5 (0.8)	
Poor outcome — no. (%)	19 (39.6)	198 (32.8)	OR, 1.32; 95% CI, 0.72–2.42; P=0.36
Defaulted‡	3 (6.2)	62 (10.3)	
Treatment failed§	5 (10.4)	13 (2.1)	
Died	11 (22.9)	123 (20.4)	
Time to interim response and to response at end of treatment — median (95% CI)			
No. of days to culture conversion	90 (57–115)	61 (59–67)	HR, 0.63; 95% CI, 0.45–0.89; P=0.008
No. of months to cure	26.0 (24.6–27.8)	24.8 (24.5–25.2)	HR, 0.83; 95% CI, 0.56–1.21; P=0.33

* Effect estimates are for the group of patients with extensively drug-resistant (XDR) tuberculosis as compared with the group that had multidrug-resistant (MDR) tuberculosis. The odds ratio (OR) and the hazard ratios (HR) are unadjusted. Outcomes were not available for five patients, all of whom had MDR tuberculosis; four transferred out of the program and one remained in treatment. P values for the OR and the HRs were calculated with the use of the chi-square test.

† Patients who completed treatment are defined as those who finished treatment according to protocol but who did not meet the definition for cure or treatment failure owing to lack of bacteriologic results (i.e., fewer than five cultures were grown in the final 12 months of therapy).

‡ Treatment default was defined as the failure of attempts to return to therapy patients who were not adhering to their treatment regimens.

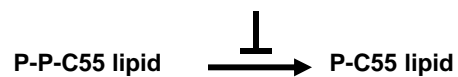
§ Treatment was considered to fail for those patients who had two or more positive cultures among the five cultures recorded in the final 12 months of the study or for whom any one of the final three cultures was positive.

Extensively drug-resistant tuberculosis can be cured in HIV-negative patients through outpatient treatment, even in those who have received multiple prior courses of therapy for tuberculosis.

Summary

TB, caused by *Mycobacterium tuberculosis*
affects lung, kidney, skin, Bone

Combinatorial treatment therapy plus Interferon- γ

Bacitracin**Mechanism:**

Antibacterial Activity: Gram (+) cocci and bacilli.

Use:

Restricted to topical use i.e. skin and eye infections

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Leprosy

Mycobacterium leprae

chronic ID

skin, peripheral nerves and mucous membranes
(eyes, respiratory tract).

also known as **Hansen's disease** as bacillus causing it
was discovered by G.A. Hansen in 1873.

common in warm, wet areas in the tropics & subtropics.



Picture 3. **Chronic insensate patch due to leprosy infection.** Ho Chi Minh City, Vietnam. (Courtesy of D. Scott Smith, MD)



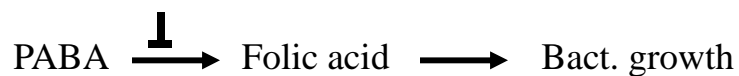
Picture 7. Man with **advanced deformities caused by unmanaged leprosy.** Keratitis, loss of eyebrow, thickened skin, and typical hand impairments. Ho Chi Minh City, Vietnam. (Courtesy of D. Scott Smith, MD)

Multidrug therapy

Sulphones
Rifampin
Clofazimine

Sulfones (Dapsone) (Alvosulfon) [bacteriocidal and bacteriostatic].

I. Mechanism similar to Sulphonamides

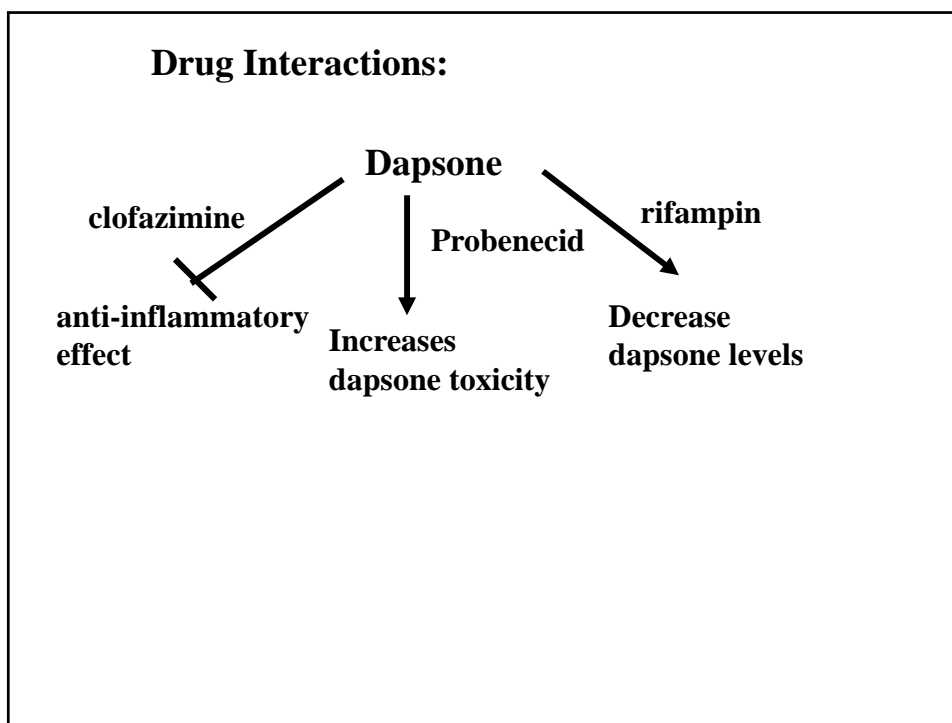


II. Absorption, Distribution, and Excretion

Rapidly absorbed, peak conc in plasma between 2-8 hr
70-80% excreted in urine

III. Untoward Effects

- Hemolysis (hemolytic anemia)
- Anorexia, nausea, vomiting
- Skin rashes,
- Sulphone syndrome: fever, jaundice, malaise
- exacerbation of lepromatous leprosy by inducing endotoxin formation



Rifampin (Rifadin, Rimactane)

Clofazimine (Lamprene)

I. Mechanism

inhibits DNA-dependent RNA polymerase

II. Absorption, Distribution, Excretion

rapidly absorbed, accumulates in tissue

II. Untoward effects

Skin discoloration,
eosinophilic enteritis
occasional GI intolerance

Other Drugs

Thalidomide

immunomodulatory, inhibits $\text{TNF}\alpha$, not
known for leprosy

Ethionamide

can substitute Clofazimin