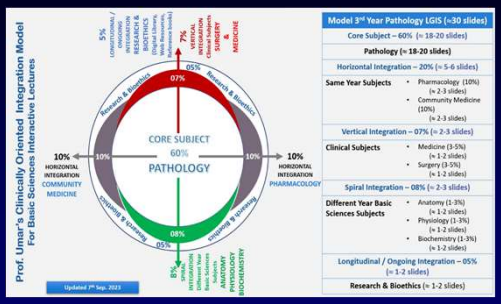
ANTI-MYCOBATERIAL DRUGS

Sources:

- Bertram G. katzung Basic & Clinical Pharmacology 15th Edition
- Goodman and Gilman's The Pharmacological Basis of Therapeutics13th edition. Laurence Brunton, Bjorn Knollmann, Randa Hilal-Dandan - (2017)

UMAR'S MODEL OF INTEGRATION



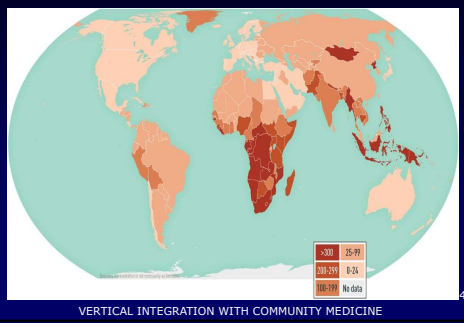
2

LEARNING OBJECTIVES

- Recall the pathophysiological mechanism of Tuberculosis
- Identify the particular characteristics of Mycobacterium tuberculosis
- Classify the drugs used in the treatment of tuberculosis
- Discuss the salient pharmacokinetic and pharmacodynamic features of anti mycobacterial drug
- Recognize the major organ toxicities of first line ATT
- Identify the clinical utility of second line ATT

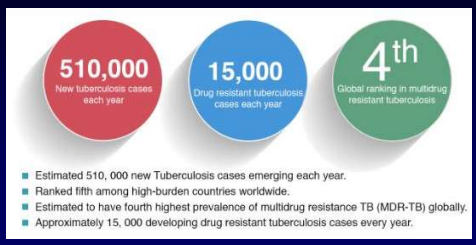
3

Estimated tuberculosis incidence rates per 100,000 population



VERTICAL INTEGRATION WITH COMMUNITY MEDICINE 4

PAKISTAN'S HIDDEN PANDEMIC



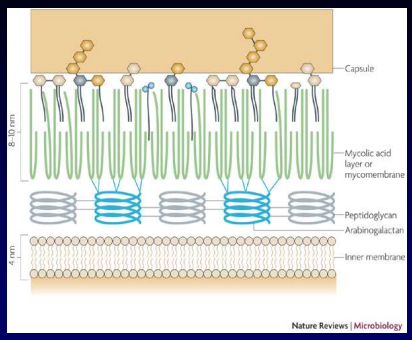
- Estimated 510, 000 new Tuberculosis cases emerging each year.
- Ranked fifth among high-burden countries worldwide.
- Estimated to have fourth highest prevalence of multidrug resistance TB (MDR-TB) globally.
- Approximately 15, 000 developing drug resistant tuberculosis cases every year.

VERTICAL INTEGRATION WITH COMMUNITY MEDICINE 5

Some Special features of *M. Tuberculosis*

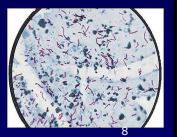
1. Intracellular (difficult to reach)
2. Dormant (difficult to reach)
3. Slowly replicating / (relatively rapid growers)
4. Cell wall made of mycolic acid/lipids (impermeable)
5. AFB…….Efflux pump present inherently.
6. Develops Resistance rapidly to single drug
7. Difficult to culture.
8. Cell wall is rich in lipids and drugs has to penetrate it.

HORIZONTAL INTEGRATION WITH PATHOLOGY 6



Some Strains of Mycobacterium

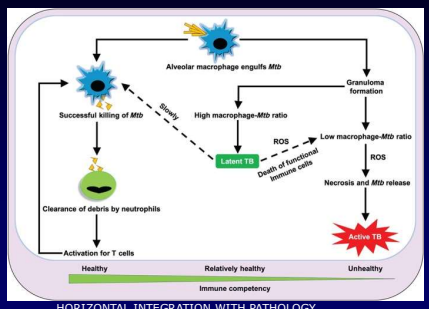
- *M. Tuberculosis*
- *M. Bovis*
- *M. Scroflaceum*
- *M. Fortuitum*
- *M. Kansasii*
- *M. Chelonae*
- *M. Ulcrans*
- *M. Marinum*
- *M. Avium*
- *M. Avium complex*
- *M. Leprae*



Virtually any organ can be involved.

- Lungs
- Lymph nodes
- Intestines
- liver
- Bones
- Skin
- F. Tube
- Ovaries
- Testis
- Kidneys
- Bladder
- Epididymus

PATHOPHYSIOLOGICAL MECHANISM



HORIZONTAL INTEGRATION WITH PATHOLOGY

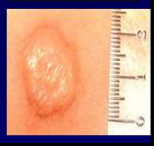
10

Diagnosis

Koch's Disease or Pulmonary Koch's

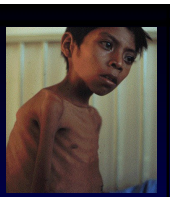
- History
- Symptoms
- Signs
- Mantoux test
- Sputum exam & culture
- Chest x-ray

Mantoux Test



PROPHYLAXIS

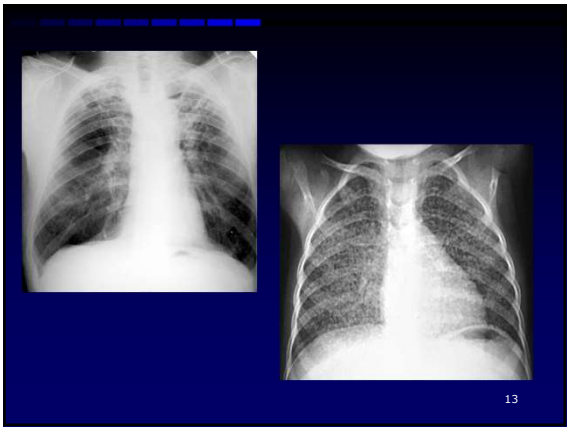
- BCG Vaccination
- INH prophylaxis to vulnerable persons.



- *Incidence increasing*----------
- *Refugees* \
- HIV
- Starvation
- Immunocompromised
- contacts

AIDS
Radiotherapy
Immunosuppressants
Corticosteroids
Malnutrition
anticancers

12



13

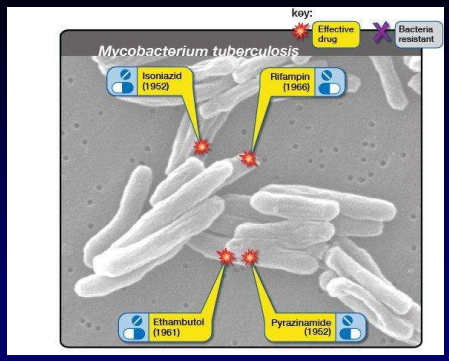
Special features of Anti-TB Treatment

1. Longer duration of treatment
2. Quick development of Resistance
3. Multi-drug therapy (in combination) indicated so
4. Various regimens of drugs used
5. Duration of therapy dependent on the organ involved
6. Duration of treatment also depends upon the drugs used in a regimen.

14

Anti Tubercular Drugs

15



16

Classified into two groups.

A . **First line Drugs**

1. Isoniazid (INH)
2. Rifampicin
3. Pyrazinamide
4. Ethambutol

Core -Pharmacology 17

II. Second Line Drugs

- Stretomycin, Kanamycin,Amikacin
- Capreomycin
- Ethionamide
- Para-aminosalicylic acid
- Cycloserine
- Ciproflaxacin / Levofloxacin
- Macrolides
- Beta lactam anti-microbials
- Clofazimine
- **Linezolid***
- **Bedaquiline***
- **Pretomanid, Delaminid***

Core -Pharmacology 18

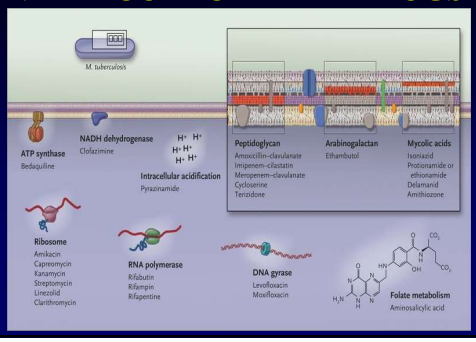
Table 1. Antituberculosis Drugs Used in the U.S.

Drug	Dosage Formulation(s) Available in U.S.
First-Line Agents	
Isoniazid[a]	Tablets, IV/IM injection
Rifampin[a]	Capsule, IV injection
Rifapentine[a]	Tablet
Rifabutin	Capsule
Ethambutol[a]	Tablet
Pyrazinamide[a]	Tablet
Second-Line Agents	
Streptomycin[a]	IV/IM injection
Amikacin	IV/IM injection
Capreomycin[a]	IV/IM injection
Ethionamide[a]	Tablet
Cycloserine[a]	Capsule
p-Aminosalicylic acid[a]	Granules
Levofloxacin	Tablet, IV injection
Moxifloxacin	Tablet, IV injection

[a] *FDA-approved for TB. Source: References 9, 10.*

19

SITE OF ACTION OF ANTIMYCOBACTERIAL DRUGS



Isoniazid (INH) Nydrazid

Synthesized in 1952. Primary anti T.B drug.

Chemistry:

Hydrazide of Iso-nicotinic acid . MW = 137

Isonicotinylhydrazide (INH)

Structure is similar to pyridoxine.

Core -Pharmacology

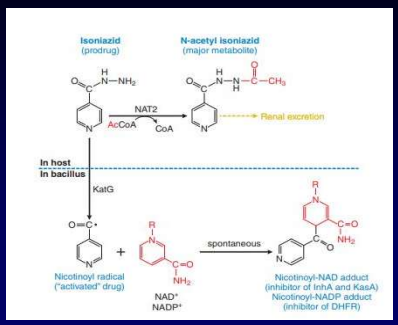
21

MECHANISM OF ACTION

- Inhibition of synthesis of mycolic acid in bacterial cell wall.
- INH is activated by mycobacterial *kat G* catalase – peroxidase
- Nicotinoyl-NAD inhibits
  - enoyl acyl carrier protein reductase (InhA)
  - β-ketoacyl acyl carrier protein synthase (KasA)

  ---- Inhibit mycolic acid synthesis → bacterial cell death.
- Nicotinoyl-NADP inhibits
  - Bacterial dihydrofolate reductasec (DHF) Enzyme ---Blocks nucleic acid synthesis

MECHANISM OF ACTION



MECHANISM OF ACTION

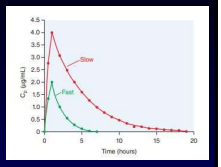
- Highly selective for *M.tub.*
- Most of atypical ones are resistant to INH.
- Bacteriostatic in low conc:
- Bacteriocidal in high conc:
- Active against both intracellular and extracellular mycobacteria.

RESISTANCE

- Increased levels of product of *inh* A gene.
- Mutation for deletion of *kat* G *(encodes bact catalase)*

- Absence of catalase leads to resistance.

PHARMACOKINETICS



- Well absorbed orally
- PP levels reached within 2 hrs
- Well distributed to all tissues
- Crosses BBB
- Acetylated in liver (Fast & Slow Acet)
- Fast acetylators are dominant trait
- Slow acet is recessive trait.
- Excreted 95 % in urine

PHARMACOKINETICS

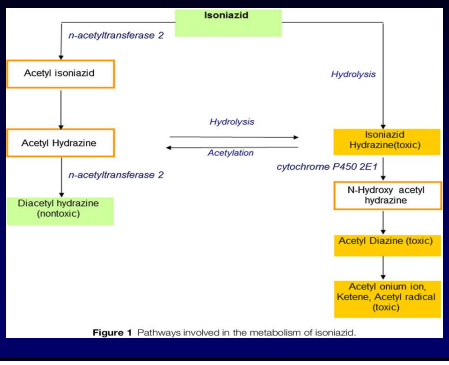


Figure 1 Pathways involved in the metabolism of isoniazid.

THERAPEUTIC USES

2-5 mg /Kg / day

I. **For Treatment of T.B: in combination for Many forms of TB.**

II. **For Prevention of TB : as single agent**

a. Newborns

b. Immuno-compromised

c. New converters

d. (HIV & AIDS)

Advantages of Isoniazid

1. The most active drug against Myco.TB
2. High selectivity against mycobacteria
3. Bactericidal action
4. Cost-effective
5. Easily available
6. Orally administered

7. Well absorbed
8. Widely distributed in body tissues/fluids
   - ❖ Enters macrophages
   - ❖ Penetrates caseous material
   - ❖ Crosses Blood-Brain Barrier
9. Single dose administration
10. Low incidence of serious toxicity

Most important adverse effect are:

1. Isoniazid induced hepatotoxicity

1. Peripheral Neuropathy
   Prevention: by admin of *Pyridoxine 25-50 mg/day*

Other Adverse effects

3. **CNS** effects
   Mental disturbances, incoordination,
   optic neuritis and convulsions

4. **AllergicReactions:** Fever, skin rashes, Rarely SLE

5. **Inhibits the metabolism** of Phenytoin

6. **Miscellaneous:-** Hematologic abnormalities, tinnitus and gastrointestinal discomfort.

II-Rifampicin or Rafampin

- A Large molecule
- Semisynthetic
- Derivative of Rifamycin obtained from *Streptomycis Mediterranei*
- Also covers some Gram +ve, Gram –ve and enteric bacteria
- No cross resistance to other classes of anti-bacterials but exists between rifamycin derivatives.

MOA

- Binds with *β- subunit* of *bacterial DNA dependent RNA polymerase* to inhibit RNA synthesis
- Bactericidal for mycobacteria as it penetrates well into most of tissues & macrophages.

- **Resistance**
- Point mutation in *rpo* B gene.. the gene for β subunit of DNA dependent RNA polymerase enzyme, which has less affinity for drug

Ph: kinetics

- Absorbed well orally, highly lipid soluble,
- Distributed to all body tissues & fluids (CSF, saliva, tears, urine, faeces, sweat)
- Excreted in bile
- undergoes entero-hepatic circulation
- Excreted as a deacylated metabolite in faeces. (Small amount appears in urine & discolors it)
- Potent Hepatic microsomal enzyme inducer

Dose:- 10 mg /kg/day or 600 mg /day for 6 months

TABLE 60–3 ■ PHARMACOKINETIC PARAMETERS OF RIFAMPIN, RIFABUTIN, AND RIFAPENTINE

	RIFABUTIN	RIFAMPIN	RIFAPENTINE
Protein binding (%)	71	85	97
Oral bioavailability (%)	20	68	–
t_{max} (h)	2.5–4.0	1.5–2.0	5.0–6.0
C_{max} total (μg/mL)	0.2–0.6	8–20	8–30
C_{max} free drug (μg/mL)	0.1	1.5	0.5
$t_{1/2}$ (h)	32–67	2–5	14–18
Intracellular/extracellular penetration	9	5	24–60
Autoinduction (AUC decrease)	40%	38%	20%
CYP3A induction	Weak	Pronounced	Moderate
CYP3A substrate	Yes	No	No

Core -Pharmacology

37

Anti Bacterial Spectrum

1. *Mycobacterium T.B*
2. *Mycobacterium Leprae*
3. *Meningococcus*
4. *H. Influenzae*
5. *Staphylococci*
6. *Pneumococci*--- Penicillin resistant strains.

M.fortuitum -- highly resistant.

HORIZONTAL INTEGRATION WITH PATHOLOGY

38

Therapeutic Uses

- Mycobacterial infections → 600 mg/day (10mg/kg/day)
- Meningococcal carrier state → 600 mg bd x 2 days
- *Hemophilus influenzae* → 20mg /kg/day x 4 days
- Staphylococcal carrier state → in combination with other agent

Core –Pharmacology
Vertical integration with medicine

39

- Penicillin resistant pneumococci in meningitis
- *Staph* infections like ***prosthetic valve endocarditis*** & **osteomylitis**
- Alternative of INH prophylaxis
- Atypical mycobacterial infections

ADVERSE EFFECTS

Serious toxicity is rare.

- Hepatotoxicity …… Jaundice
- GIT upsets
- Skin rash and fever
- Flue-like syndrome
- Harmless orange discoloration of the urine, sweat, tears and contact lenses.
- Enzyme induction of many drugs, including

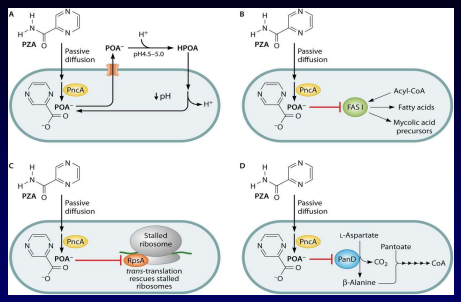
Oral Contraceptives	Warfarin
Methadone	Corticosteroids
Sulfonylureas	Digoxin

III- Pyrazinamide

It is synthetic analog of Nicotinamide.

- Slightly soluble in water
- Cheaper compound
- Active against intracellular Mycobacteria
- Inactive at neutral pH but at 5.5, it inhibits tubercle bacilli.
- It is activated by acidic conditions into Pyrazinoic acid (Active form)
- *Bactericidal*

MECHANISM OF ACTION



Resistance develop rapidly (due to mutation in *pnc* A that impair conversion of pyrazinamide to its active form)

43

Core –Pharmacology

PHARMACOKINETICS

- Absorbed readily from GIT
- Widely distributed
- t½ is 12 – 24 hrs

ADVERSE EFFECTS

- Hepatotoxicity
- Hyperuricemia → gouty arthritis
- Nausea vomiting
- Drug fever
- Malaise

44

Core –Pharmacology

Therapeutic Uses

1. Treatment of T.B in Combination with INH and Rifampicin, Ethambutol in intensive phase of regimen

Dose: **15—30 mg** /Kg/day in divided doses

45

ETHAMBUTOL

Source & Chemistry

- **1ST Synthetic anti TB Agent.**
- water soluble, heat stable

MOA

- Bacteriostatic
- Inhibits synthesis of *arabino-galactane* an essential component of cell wall of Mycobacterium (by inhibiting arabinosyl transferases)

46

Ethambutol

Ph: Kinetics

- Absorbed well orally
- PPL.. 2 – 4 hrs
- 50% excreted in urine & 20% in feces
- Cross BBB when meninges are inflamed

47

Ethambutol

- **Resistance**
- Emerges rapidly
- Mutations resulting in over expression of *emb gene products* (Arabinosyl transferases)
- Mutation within the structural gene *emb B*

Dose: **15 mg/kg/day** Orally Once daily

48

Clinical uses

- 15 -25 mg/kg/day with INH & Rifampin in pulmonary T.B.
- Higher doses for T.B. meningitis

ADVERSE EFFECTS

- Loss of visual acuity……**Retrobulbar neuritis ..**

tubular vision so contraindicated in children under 5 years.

- Loss of red – green color appreciation
- Interstitial nephritis
- Drug fever Rash,
- Confusion
- GL. Upset

49