PHARMACOTHERAPY OF TUBERCULOSIS

History

Para-amino salicylic acid --- Lehman 1943.
Thiacetazone --- Domagk in 1946
Streptomycin --- Waksman and Schatz 1947
Isoniazid --- Hoffman Roche, Bayer in 1952
Pyrazinamide --- Kushner et al in 1952
Rifamycins --- Sensi and Margalith in 1957.
Ethambutol --- Lederle Laboratories in 1961.
Bedaquiline --- Andries et al. in 2005,
Delaminid --- Matsumoto et al. in 2006

Drug	Typical Adult Dosage
First-line agents	
Isoniazid	300 mg/d
Rifampin	600 mg/d
Pyrazinamide	25mg/kg/d
Ethambutol	15–25 mg/kg/d
Streptomycin	15 mg/kg/d
Second-line agents	
Amikacin	15 mg/kg/d
Para aminosalicylic acid	8–12 g/d
Capreomycin	15 mg/kg/d
Bedaquiline: 400mg/d for 2 weeks, 200mg tds	
Delaminid	100mg bd

Drug	Typical adult dosage
Ciprofloxacin	1500 mg/d
Clofazimine	200 mg/d
Cycloserine	500–1000 mg/d
Ethionamide	500–750 mg/d
Levofloxacin	500 mg/d
Rifabutin	300 mg/d
Rifapentine	600 mg once/twice weekly
Linezolid	600mg/d
Moxifloxacin	10mg/kg/day max 400mg
Ofloxacin	Max 800mg/day
Prothionamide	15-20mg/kg/d max 1gm
Terizidone	15-20mg/kg/d max 1gm

Alternative grouping of antitubercular drugs (WHO Guidelines 2010)

Group I --- First line oral anti-TB drugs
Isoniazid (INH), Rifampin, Pyrazinamide, Ethambutol

Group II --- Injectable anti-TB drugs
Streptomycin, Kanamycin, Amikacin, Capreomycin

Group III --- Fluoroquinolones - Ofloxacin, Levofloxacin, Moxifloxacin, Ciprofloxacin

Group IV--- 2nd line oral anti-TB drugs
Ethionamide, Prothionamide, Cycloserine, Terizidone, Paraaminosalicylic acid, Rifabutin, Rifapentine.
Less effective, bacteriostatic, more toxic oral drugs for resistant TB.

Group V --- Drugs with unclear efficacy, Clarithromycin, Clofazimine, Linezolid, Amoxicillin / clavulanate, Imipenem /cilastatin
Not recommended for MDR-TB; reserve drugs for use in extensively resistant TB (XDR-TB).

Bedaquiline, **Delaminid**

Mechanisms of drug action

Isoniazid **Ethionamide** **Prothiona-mide**	Activated by KatG (myco-bacterial catalase-peroxidase). Activated form interacts with InhA and KasA gene products blocks mycolic acid synthesis and kills the cell.
Rifamycins **Rifampin** **Rifabutin** **Rifapentine**	Binds to the beta subunit of bacterial DNA-dependent RNA polymerase; inhibits RNA synthesis.

Mechanisms of drug action

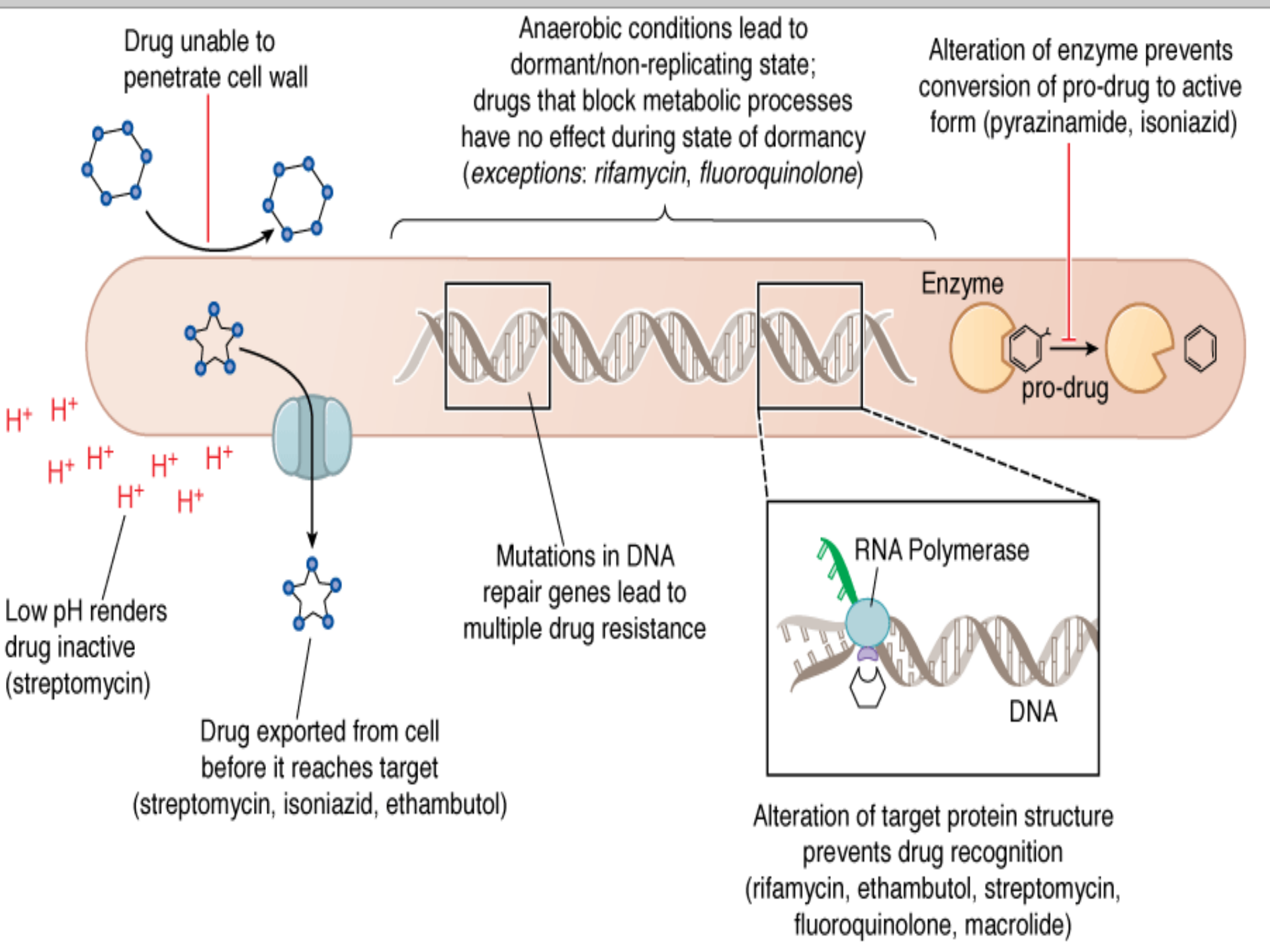
Pyra-zinamide	• Activated by low pH --- inhibits fatty acid synthase type I --- interferes with mycolic acid synthesis • Reduction of intracellular pH • Disruption of membrane transport.
Etham-butol	• Inhibits arabinosyl transferases (embAB) --- arabinogalactan synthesis --- disrupts mycolic acid incorporation in cell wall.

Mechanisms of drug action

Sreptomycin, **kanamycin** , **amikacin**, **capreomycin**	Bactericidal protein synthesis inhibitors
Moxifloxacin, Ofloxacin, Levofloxacin, Ciprofloxacin	DNA gyrase inhibitors
Cycloserine, Terizidone	Cell wall synthesis inhibitors
PAS	As sulphonamides

Mechanism of action

Bedaquiline	Targets subunit c of ATP synthase. Thus targets bacillary energy metabolism.
Delamanid/ Pretomanid	• Prodrugs: activation via nitro-reduction step. • Under aerobic conditions inhibits mycolic acid and protein synthesis. • Generate NO which augments the killing of intracellular bacilli by innate immune system.


Drug unable to penetrate cell wall
Anaerobic conditions lead to dormant/non-replicating state; drugs that block metabolic processes have no effect during state of dormancy (*exceptions*: *rifamycin*, *fluoroquinolone*)
Alteration of enzyme prevents conversion of pro-drug to active form (pyrazinamide, isoniazid)
Enzyme
pro-drug
H+
Low pH renders drug inactive (streptomycin)
Drug exported from cell before it reaches target (streptomycin, isoniazid, ethambutol)
Mutations in DNA repair genes lead to multiple drug resistance
RNA Polymerase
DNA
Alteration of target protein structure prevents drug recognition (rifamycin, ethambutol, streptomycin, fluoroquinolone, macrolide)

Isoniazid (H)

Penetrates well into caseous material. Infected tissue retains drug for a long time.

Metabolism genetically determined.

Dose adjustment in severe preexisting hepatic insufficiency.

Pyridoxine (10-50mg /day) --- minimizes peripheral neuropathy and CNS toxicity in malnourished, elderly, pregnancy, HIV-infected, diabetics, alcoholics and uremics.

Untoward Effects

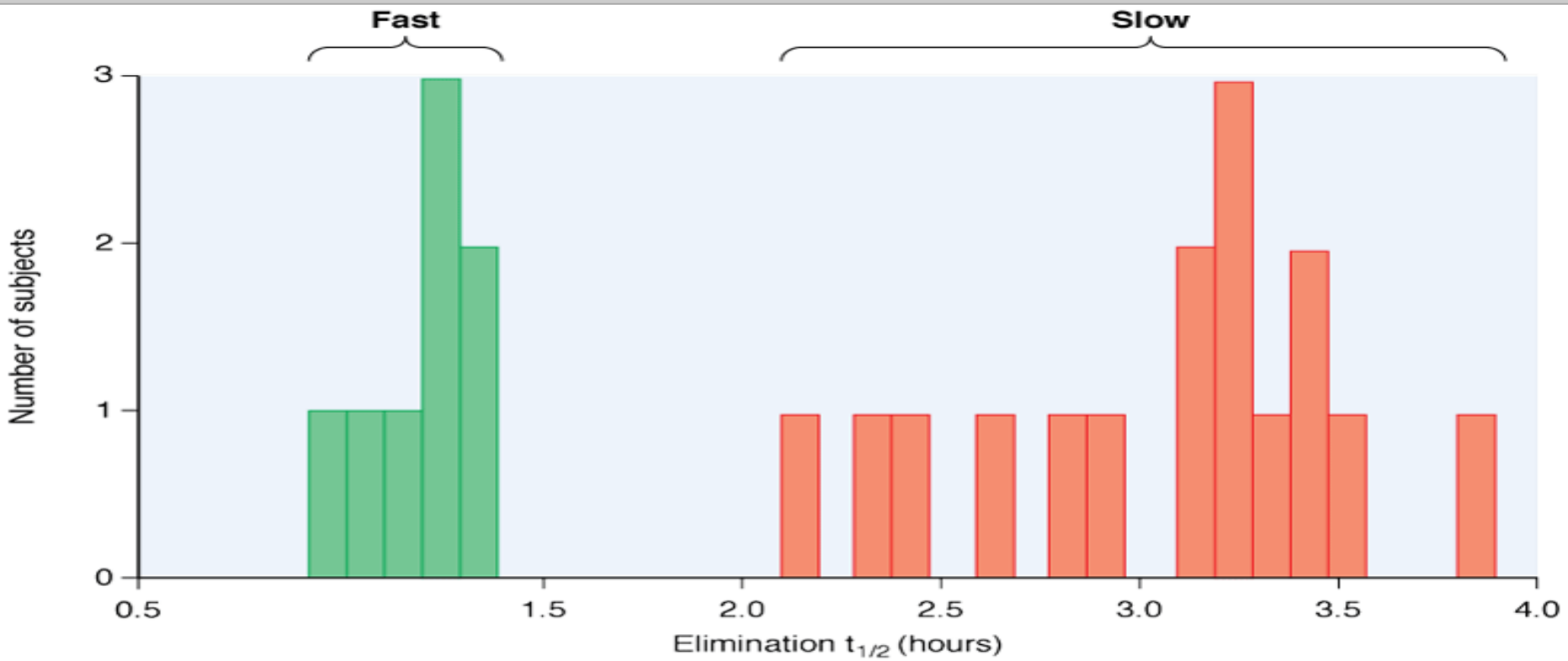
Rash, fever, jaundice, peripheral neuritis.

Hypersensitivity: fever, skin eruptions.

Arthritic symptoms: Back pain; arthralgia of the knees, elbows, and wrists.

Neurotoxicity: seizures, Optic neuritis and atrophy; Muscle twitching, dizziness, ataxia, paresthesias, stupor, toxic encephalopathy.

Jaundice: (bridging and multilobular necrosis). Mechanisms unknown. More in elderly.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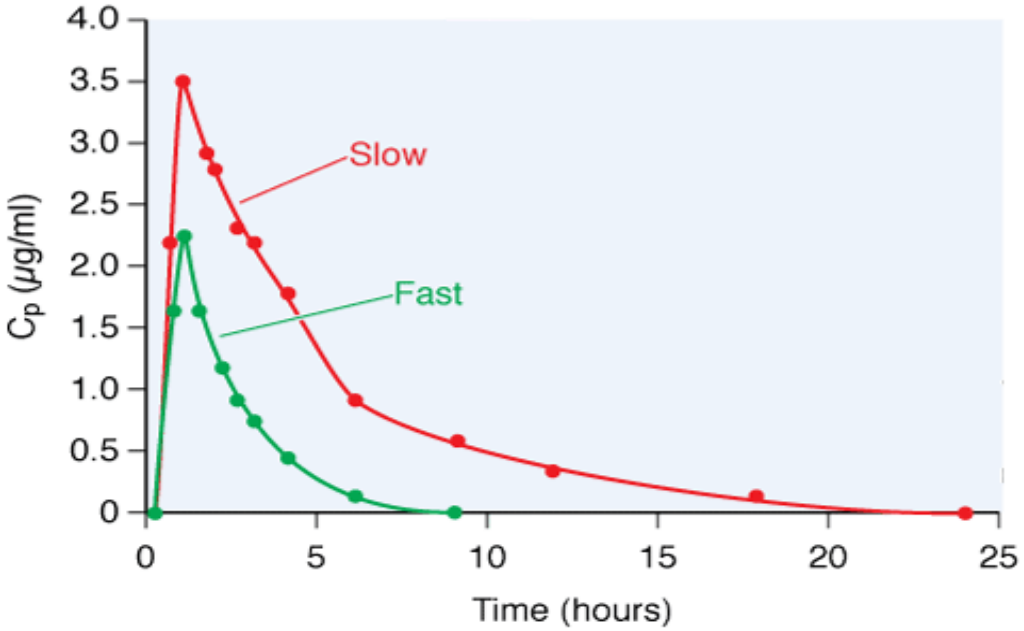
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Rifampin (R)

Inhibits --- **Escherichia coli**, **Pseudomonas**, **Proteus**, **Klebsiella, Staph aureus** and **Coagulase negative staphylococci**, **N. meningitidis** and **Haemophilus influenzae**.

No cross-resistance to other drugs; cross-resistance to Rifabutin and Rifapentine.

Prophylaxis of meningococcal disease and *H. influenzae* meningitis. Eradicates staphylococcal carriage. Combination therapy for osteomyelitis, prosthetic valve endocarditis.

Adverse effects :

Harmless **orange coloration** of urine, sweat, tears, and contact lenses (soft lenses permanently stained).

Occasional : Rashes, thrombocytopenia, and nephritis, cholestatic jaundice and hepatitis.

Flu-like syndrome : Fever, chills, myalgias, arthralgia, anemia.

Strongly induces CYPs 1A2, **2C9**, **2C19**, **2D6**, and **3A4**.

Reduces biliary excretion of contrast media.

Pyrazinamide (Z)

Synthetic pyrazine analog of nicotinamide.

Used with isoniazid and rifampin in 6-month regimens as a "sterilizing" agent active against residual intracellular organisms.

Penetration into the CSF is excellent.

Adverse Effects :

Hepatotoxicity : LFT prior to starting therapy. **Hyperuricemia**; acute episodes of gout. Arthralgias, anorexia, nausea and vomiting, malaise, and fever.

Ethambutol (E)

Synthetic, water-soluble, heat-stable.
Dose reduction in renal dysfunction.

Adverse Reactions

Optic neuritis --- **loss of visual acuity** and **red-green color blindness** (dose-related).
Periodic visual acuity testing desirable.

Decreased renal excretion of uric acid.
Rash, drug fever, pruritus, joint pain, GI upset, abdominal pain, malaise, headache, dizziness, mental confusion, disorientation.

Streptomycin (S)

Activity *in vivo* is **essentially suppressive**.

If S-resistant infection --- stop --- risk of **S dependence**

A '**supplemental' 1st line drug**.

Resistance : point mutation in *rpsL* gene, which alters the ribosomal binding site.

In severe, life-threatening forms of disease e.g. disseminated disease & infections resistant to other drugs

Ethionamide (Eto)

Moderate efficacy --- acts on both extra- and intracellular bacilli --- **only oral**.

CSF conc are equal to those in serum.

Adverse effects :

Anorexia, nausea and vomiting, neurologic symptoms relieved by Pyridoxine.

Hepatitis.

Severe postural hypotension, mental depression, drowsiness, allergic skin rashes, purpura, stomatitis, gynecomastia, impotence, menorrhagia, acne.

Capreomycin (Cm) : Peptide protein synthesis inhibitor.
Streptomycin / amikacin resistant strains susceptible. Cross-resistance with kanamycin and neomycin

Kanamycin (Km) & Amikacin (Am)
Most MDR strains susceptible.
No cross-resistance with streptomycin.

Nephrotoxic & ototoxic. Tinnitus, deafness, vestibular disturbances occur. Injection site --- local pain and sterile abscesses.

Cycloserine (Cs)

Reduce dose in renal dysfunction.
No cross-resistance with other agents. CSF concentration same as in plasma.

Adverse effects

Peripheral neuropathy and CNS dysfunction --- **depression and psychotic reactions**.
Pyridoxine 100 mg/d for neurologic toxicity.
Contraindicated in epilepsy and depression, as suicide is a risk.

Para aminosalicylic Acid (PAS) :
Bacteriostatic.

High conc in pleural fluid and caseous tissue but CSF levels are low.

Gastrointestinal problems : anorexia, nausea, epigastric pain, abdominal distress and diarrhoea. High conc --- crystalluria.

Hypersensitivity reactions : fever, joint pains, skin rashes, hepatosplenomegaly, hepatitis, lymphadenopathy and granulocytopenia

Fluoroquinolones

Ofloxacin **(Ofx)**, levofloxacin **(Lvx),** ciprofloxacin **(Cfx)** and moxifloxacin **(Mfx).** Active against MAC, M. fortuitum, other atypical mycobacteria.

Mfx most active, Lvx is more active than Ofx and Cfx. Cfx is more active against atypical mycobacteria.

Tried in 1st line regimens for new cases to accompany RHZ --- enhance bacillary killing and cause faster sputum conversion.

Prothionamide (Pto)

Interchangeable with ethionamide.

Terizidone

- It contains 2 molecules of cycloserine
- Less neurotoxic
- Incidence of adverse effects lower.
- Used as a substitute for Cs, in genito-urinary TB --- attains higher and longer lasting concentration in urine.

Rifabutin

Less potent inducer for HIV patients on antiretroviral therapy with a protease inhibitor or NNRTIs (eg, efavirenz)—drugs that are cytochrome P450 substrates.

Rifapentine

Potent inducer of cytochrome P450 enzymes. Not for HIV-infected patients --- unacceptably high relapse rate with rifampin-resistant organisms.

Cross-resistance with rifampin with both.

Linezolid, Tedizolid, and Sutezolid
Achieve good intracellular concentrations. Extremely high sputum conversion rates, but at a price of a high rate of adverse events.

Treatment limiting adverse effects
Bone marrow suppression and irreversible peripheral and optic neuropathy.

Interferon-g (IFN-g)
Aerosol delivery to lungs in MDR TB results in wide pulmonary distribution and **enhanced local immune stimulation**

Nitroimidazoles: Delaminid / Pretomanid

Used in the treatment of XDR and MDR TB and also drug-susceptible TB (clinical trials).

ADME

Bioavailability increases with food intake.

Untoward Effects

Delamanid is associated with QT segment prolongation; however, the clinical significance is unclear.

Bedaquiline

For XDR, MDR and difficult to treat cases.

Antibacterial Activity

Good activity against M. leprae, MAC and miscellaneous atypical mycobacteria.

ADME --- poor CNS concentration, Fatty meal improves absorption.

Untoward Effects: nausea, diarrhea, arthralgia, pain in extremities, hyperuricemia. Major concern --- **cardiovascular toxicity and death**. Increased corrected QT interval.

General guidelines for use of Bedaquiline

1. Only for **pulmonary MDR TB** in adults.
2. Women should avoid pregnancy while on this drug.
3. In combination with at least 3 other anti TB drugs to which patient is sensitive.
4. Only when an effective regimen otherwise cannot be provided.
5. Should be given for maximum 24 weeks.
6. Each tablet to be swallowed whole with meals.
7. The other combination drugs to be continued for 2 years after stopping it.

GENERAL GUIDELINES

- Kill the dividing and persisting bacilli.
- Rationale for multidrug therapy --- prevent emergence of resistance.
- Directly observed treatment strategy **(DOTS).**
- Conventional regimes (12 – 18) months.
- Short course chemotherapy (6 – 9) months.
- Initial Intensive phase (2- 3) months and continuation phase (4 – 6) months

Drug sensitive TB : susceptible to all 1st line.
MDR TB: Resistance to R and H + any number of 1st line drugs.
Rifampin resistant TB: Resistant to R but not H with or without resistance to other ATDs. To be treated like MDR TB.
Monoresistant TB: Bacilli are resistant to one first line ATD but not R resistant.
Poly drug resistant TB: Bacilli are resistant to more than one 1st line ATD except both R and H.
XDR TB: MDR patients additionally resistant to a fluoroquinolone and one 2nd line injectable.

Drug Sensitive TB

New patients

Intensive phase (IP)	Continuation phase (CP)	Duration
2HRZE	4HRE	6 months*

Previously Treated

2HRZES + 1HRZE	5HRE	8 months *

Drugs to be taken on a daily basis

* Optimal According to RNTCP guidelines 2016

Continuation Phase may be extended by 3-6 months on clinical grounds

MDR Tuberculosis

Intensive phase (6–9 months)

1. Kanamycin (Km)
2. Levofloxacin (Lfx)
3. Ethionamide (Eto)
4. Cycloserine (Cs)
5. Pyrazinamide (Z)
6. Ethambutol (E)

+ Pyridoxine 100 mg/day

Continuation phase (18 months)

1. Levofloxacin
2. Ethionamide
3. Cycloserine
4. Ethambutol

Individualised treatment as required

Rifampin resistant TB

- Treated the same way as MDR TB.
- INH can be added to the MDR regimen both in the intensive as well as continuation phase without changing the duration of other drugs.

Mono drug resistant tuberculosis

- R + 2 oral 1st line drugs to which bacilli are sensitive + 1 injectable 2nd line drug + 1 fluoroquinolone = 5 drugs given daily in the intensive phase of 3-6 months.
- All except injectable in continuation phase of fixed 6 months.

Poly drug resistant TB

Initial Regimen is R + 1 injectable 2nd line drug + 1 fluroquinolone + any one 1st line drug to which the bacilli is sensitive + 1 oral 2nd line drug(Eto/Cs/PAS) the duration of intensive phase is 3-6 months.

In the continuation phase the injectable drug is stopped and remaining 4 oral drugs are given for a fixed duration of 6 months.

Thus total duration of both mono and polydrug resistant TB is 9-12 months

Isoniazid resistant TB

In low level resistace: High dose INH 900mg / day for 46 to 70kg weight instead of 300mg / day. Along with pyridoxine. In high level resistance it should not be given.

Extensively Drug resistant tuberculosis

MDR regimen immediately stopped.

7 drugs in IP (6-12 months); 6 drugs in CP (18months). Capreomycin, moxifloxacin, high dose isoniazid, PAS, Clofazimine, Linezolid, Amoxicillin + clavulinic acid. Discontinue Cm in CP.

PREGNANCY

2HRZE + 4 HRE

All 4 oral 1st line drugs are safe.

All to receive pyridoxine 10-25mg daily.

Breastfeeding

All 4 1st line oral drugs compatible with breast feeding

Infant should receive 6 month INH prophylaxis with Pyridoxine 5mg/day after ruling out active TB followed by BCG vaccination.

Management of ADRs

Ethambutol --- discontinue if **optic neuritis**.

Severe Hypersensitivity --- Discontinue all and introduce one by one gradually.

Hepatotoxicity --- stop all drugs --- reaction allowed to subside. If TB is severe --- S + E + One FQ started while the reaction clears.

Z responsible --- HRE for 9 months.
R responsible --- 2HES followed by 10HE.
H implicated --- REZ for 9 months.
If both R & H---S,E,FQ for 18–24 months.

Chemoprophylaxis

- Contacts of open cases with recent mantoux conversion.
- Children with a sputum + ve TB patient in the family.
- Infant born to a tubercular mother.
- Contacts with diabetes, leukaemia, silicosis, HIV or on long term immunosupressants.
- INH 300mg daily (10mg/ kg in children) for 6 months. Once a week Rifapentine (10mg/kg) + high dose INH (15mg/kg) given for 3 months.

Role of corticosteroids

(a) In seriously ill patients (miliary or severe pulmonary TB) to buy time for drugs to act.

(b) When hypersensitivity reactions occur to antitubercular drugs.

(c) In meningeal /renal /pericardial TB or pleural effusion—to reduce exudation, prevent its organisation and strictures, etc.

(d) In AIDS patients with severe manifestations of tuberculosis.

TB in HIV patients

- HIV infection is the strongest risk factor for unmasking latent TB.
- Higher incidence of extrapulmonary, more severe, more lethal and more infectious TB.

2HRZE 4-7HRE (Total 6-9 months) + Pyridoxine 25 – 50 mg / day plus **Cotrimoxazole** preventive therapy through out the course (Pneumocystis jiroveci).

MDR TB in HIV patients treated for total 24 months same as in non HIV.

MAC Infection

Intensive phase (2 to 6 months)

1. **Clarithromycin** 500 mg twice daily or **Azithromycin** 500 mg once daily
2. **Ethambutol** 1000 mg (15 mg/kg) per day
3. **Rifabutin** 300 mg per day
4. **Ciprofloxacin** 500 mg twice daily or **Levofloxacin** 500 mg once daily or **Moxifloxacin** 400 mg once daily

Maintenance phase (minimum 12 months)

1. Clarithromycin /Azithromycin
2. Ethambutol/Rifabutin/One fluoroquinolone

Prophylaxis of MAC infection

- To protect AIDS patient from developing active MAC disease when CD4 count is below 75 cell/μL.
- A single drug is used
- Azithromycin 1200 mg/week or clarithro-mycin 500 mg twice a day are preferred drugs.
- Rifabutin 300 mg/day is used if either of these drugs cannot be given.
- Continued till simultaneously instituted ART achieves complete suppression of HIV replication, CD4 count rises above 100 cell/μL and stays there for at least 3 months.

PHARMACOTHERAPY OF LEPROSY

Progress in chemotherapy slow, inefficient animal models and methods of diagnosis

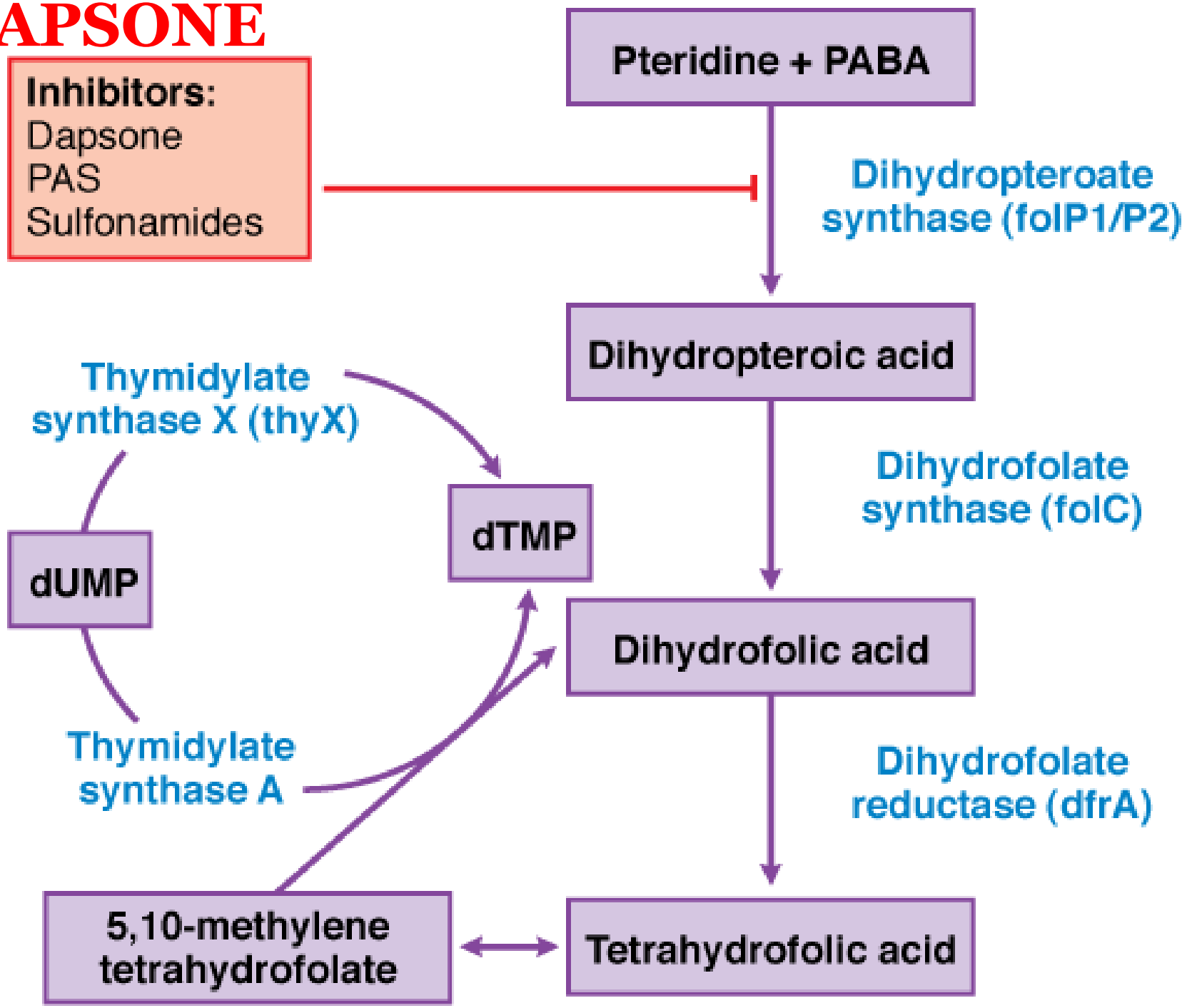
Chronic and slowly progressive disease

Inadequate treatment / control measures

1ST Line Drugs : Dapsone , Rifampicin, Clofazimine

2ND Line Drugs : Ofloxacin, Moxifloxacin, Minocycline, Clarithromycin, Ethionamide

DAPSONE


Inhibitors:
Dapsone
PAS
Sulfonamides
Pteridine + PABA
Dihydropteroate synthase (folP1/P2)
Dihydropteroic acid
Dihydrofolate synthase (folC)
Dihydrofolic acid
Dihydrofolate reductase (dfrA)
Tetrahydrofolic acid
5,10-methylene tetrahydrofolate
Thymidylate synthase A
dUMP
Thymidylate synthase X (thyX)
dTMP

DAPSONE (50 – 100 mg OD)

Anti-inflammatory effects via inhibition of tissue damage by neutrophils.

- Inhibits neutrophil myeloperoxidase activity and respiratory burst.
- Inhibits activity of neutrophil lysosomal enzymes.
- Act as a free radical scavenger.
- Inhibit migration of neutrophils to inflammatory lesions.

DAPSONE

Bacteriostatic; weak bactericidal activity

Antibacterial: M. leprae, MAC and M. kansasii.

Anti-Parasitic: Plasmodium falciparum even in sulfadoxine-pyrimethamine–resistant strains. Toxoplasma gondii tachyzoites.

Antifungal: Pneumocystic jiroveci

Concentrated in skin (especially lepromatous skin), muscle, liver and kidney

Limitations : resistance

Contraindications : hemoglobin less than 7gm%, history of hypersensitivity and G6PD deficiency

Safe in pregnancy

Drug Interaction with Probenecid

ADRs: Hematological and dose related haemolytic anaemia in Patients with G6PD deficiency ; allergic reactions; rarely exfoliative dermatitis; mild GIT symptoms.

SULPHONE SYNDROME

CLOFAZIMINE (300mg once a month + 50mg daily)

Leprostatic and Antiinflammatory

- Interference with template function of DNA in M.leprae
- Alteration of membrane stucture and its transport function.
- Disruption of mitochondrial electron transport chain.

- A component (MDT) of leprosy, MDT of MAC infection, MDT of XDR TB.
- Valuable in lepra reaction.

Adverse effects: Reddish black pigmentation of the exposed parts of the body, conjunctiva and body secretions.

Dryness of skin, itching, scaling and photo-toxicity. GIT symptoms --- nausea loose stools , abdominal pain, anorexia and weight loss.

Expensive compared to Dapsone

Contraindications

Early pregnancy, liver and kidney damage

Not safe in pregnancy

Rifampin (R)

(600mg monthly dose)

- Potent cidal drug for M.leprae.
- Clinical effects very rapid; nasal symptoms in LL subside by 2–3 weeks and skin lesions start regressing by 2 months.
- Included in MDT to shorten duration of treatment and delay resistance.
- Remains effective even if given once a month.
- Should not be given in hepatic or renal dysfunction, in 'erythema nodosum leprosum' (ENL) and 'reversal reaction' in leprosy.

Ethionamide (250 mg/day)

- poorly tolerated used only when absolutely necessary.

Ofloxacin (400 mg/day)

- used most as a component of MDT.
- Not yet included in standard MDT, can be an alternative if rifampin cannot be used.
- Moxifloxacin also potent.

Minocycline (100 mg/day)

- Antileprotic activity is less marked than rifampin, but greater than clarithromycin.
- Vertigo only on long-term use.
- Being tried in alternative MDT regimens.

Clarithromycin (500 mg daily)

- **O**nly macrolide with significant activity against M. leprae.
- Less bactericidal than rifampin.
- A synergistic action with minocycline has been demonstrated.
- Being included in alternative MDT regimens.

Child doses:

Rifampin: 10mg/kg once monthly

Clofazimine: 1mg/kg daily+ 6mg/kg once a month

Dapsone: 2mg/kg daily

Tuberculoid	Lepromatous
Anaesthetic patch	Diffuse skin & mucous membrane infiltration, nodules
CMI is normal	CMI is absent
Lepromin test +ve	Lepromin test -ve
Bacilli rarely in biopsies	Skin and mucous membrane full of bacilli
Prolonged remissions with periodic exacerbations	Anaesthesia of distal parts, atrophy, ulceration, absorbed digits

Paucibacillary (PB)	**Multibacillary(MB)**
• 1-5 skin lesions • No nerve/ only 1 nerve ± 1–5 skin lesions. • Skin smear negative at all sites.	6 or more skin lesions > 1 nerve involvement irrespective of number of skin lesions Skin smear positive at all sites.

Multidrug Therapy (MDT) for Leprosy

Multibacillary Leprosy

Rifampicin 600mg once a month supervised
Dapsone 100mg daily self administered
Clofazimine 300mg once a month supervised;
50mg daily self administered

Duration --- 12 months

Paucibacillary Leprosy

Rifampicin 600mg once a month supervised
Dapsone 100mg daily self administered

Duration --- 6 months

Relapse of leprosy

Same MDT, 12 months for MBL and 6 months for PBL on confirmation of relapse

Leprosy + TB coinfection

MDT for leprosy continued, but Rifampin given daily for TB.

Leprosy in HIV patients

Association not found. MDT for leprosy may be given with antiretroviral therapy.

Alternative regimens :

- **Intermittent ROM**: **Rifampin** *600 mg* + **Ofloxacin** *400 mg* + **Minocycline** 100 mg once a month for **3–6 months for PBL** and for **12 or 24 months for MBL** cases, without any drug in between.

- **Cloflazimine** 50 mg + **any two** of **ofloxacin** 400 mg**/minocycline** 100 mg**/clarithromycin** 500 mg **daily for 6 month**, followed by **clofazimine** 50 mg + **any one** of **ofloxacin** 400 mg **/minocycline** 100 mg **daily for additional 18 months.**

• **Four drug regimen** of **Rifampin** 600 mg + **Sparfloxacin** 200 mg + **Clarithromycin** 500 mg + **Minocycline** 100 mg **daily for 12 weeks in MBL**.
• In case of refusal to accept clofazimine: ofloxacin 400 mg or minocycline 100 mg daily in standard MDT.

Intermitent RMMx: **Moxifloxacin** *400 mg* + **Minocycline** 200 mg + **Rifampin** 600 mg is administered **once a month**: **6 doses for PBL** and **12 doses for MBL cases**.

Doses to be reduced for children

Reactions in leprosy

Lepra reaction : Jarish Herxheimer type of reaction

Clofazimine 200mg daily, Prednisolone 40 – 60 mg /day continued till reaction subsides and then gradually tapered over 2-3 months.

NSAIDS / Cloroquine 150mg base TDS for 2 weeks / Thalidomide 400mg /day

Reversal reaction : Delayed Hypersensitivity type of reaction. Treated with clofazimine and corticosteroids but thalidomide ineffective.