INTRODUCTION

- *Mycobact. tuberculosis* - chronic grannulomatous disease – major health problem
- 1/3rd of world`s population and 10 - 15%
- India – 2.2 million patients were suffering from TB in 2016 and up to 4.23 lakh died
- National Tuberculosis Programme of India – 1962
- Revised National Tuberculosis Control Programme 1997
- Nation wide coverage of DoT therapy 2006 - Notifiable disease 2012 – treatment guidelines 2016
- NATIONAL STRATEGIC PLAN (NST) FOR TUBERCULOSIS ELIMINATION 2017–2025 – Decline burden, morbidity, motality and elimination
- Mycobact. avium complex (MAC), MDR TB and XDR TB

DRUGS FOR TB

- **First Line:** High efficacy – low toxicity – routinely used
- *Streptomycin (S)* 1947
- *Isoniazid (H)*1952
- *Ethambutol (E)* 1961
- *Rifampicin (R) 1962*
- *Pyrazinamide (Z)* 1970

- **Second Line:** Low antitubercular efficacy and/or higher toxicity – reserve drugs:
  - Ethionamide (Eto), Prothionamide (Pto), Cycloserine (Cs), Terizidone (Trd), Para-aminosalicylic acid (PAS), Rifabutin, Rifapentine
  - **Fluoroquinolones:** Ofloxacin (Ofx), Levofloxacin (Lvx/Lfx), Moxifloxacin Mfx), ciprofloxacin (fx)
  - **Injectables:** Kanamycin (Km), Amikacin (Am), Capreomycin (Cm)

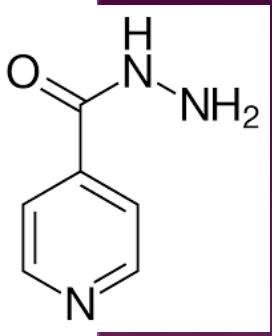
ALTERNATIVE GROUPING

- **Group I:** Isoniazid, Rifampicin, Pyrazinamide and Ethambutol
- **Group II:** Streptomycin, Kanamycin, Amikacin and apreomycin
- **Group III:** Ofloxacin (Ofx), Levofloxacin (Lvx/Lfx), Moxifloxacin Mfx), ciprofloxacin (fx)
- **Group IV:** Ethionamide (Eto), Prothionamide (Pto), Cycloserine (Cs), Terizidone (Trd), Para-aminosalicylic acid, Rifabutin, Rifapentine
- **Group V:** Bedaquiline, larithromycin, lofazimine, Linezolid, Coamoxiclav and Imipenem/cilastin

ISONIAZID (ISONICOTINIC ACID HYDRAZIDE)

- INH (H) first line anti-TB drug
- Excellent and essential component – unless resistance or intolerability
- Tuberculocidal – fast multiplying organisms – quiescent ones ?
- Extracellular as well as intracellular – also acidic and alkaline medium
- Cheapest – nontubercular mycobacteria?

INH - CONTD.



- **MOA:** Inhibition of synthesis of mycolic acid – unique fatty acid in mycobacterial cell wall - lipid content of mycobacteria reduced
  - Genes "InhA" and "KasA" are targetted
  - INH enters mycobacteria – converts to active metabolinte by *catalase peroxidase (KatG)* enzyme
  - Adducts with NAD and inhibits "InhA" and "KasA"
  - Also adducts with NADPH – DHFRase inhibition – no DNA
- **Resistance:**
  - 1 in 10^6 inherently resistant - given alone ?
  - Mutation of *KatG*
  - Mutation of "InhA" and "KasA"
  - Efflux of INH and its concentrating mechanism
- **Kinetics:** Complete absorption orally – all tissues, cavities, meninges, placents
  - N-acetylation by NAT2 (urine)
  - Fast acetylators and slow acetylators - biweekly regime?
  - 1 hr Vs 3 hours half-life
  - CYP2E1 Acetylhydrazine - hepatotoxic

INH - CONTD.

- **Drug interactions:** Aluminium hydroxide (AlOH)
  - Retards metabolism - Phenytoin, carbamazepine, diazepam, theophylline – CYP2C19 and CYP3A4
  - Concurrent Rifampicin?
- **ADRs:**
  - Peripheral neuropathy – numbness, parasthesia, mental disturbance & convulsion – dose dependent
    - Why ? – pyridoxal + INH (hydrazone) – pyridoxal PO4 not formed from pyridoxine
    - Prophylactic pyridoxine (10 mg/day) – special group
  - Hepatitis – elderly and alcoholics (CYP2E1 induced)
  - Lethargy, rash, fever, acne and athralgia

RIFAMPICIN (R)

- Source – derivative of Rifamycin B – obtained from *Streptomyces mediterrani*
- Bactericidal to M. tuberculosis and may other gm+ve and –ve bacteria – Staph. aureus, E. coli, M. Leprae, Pseudomonas, Proteus etc.
- Efficacy same as INH – Better than all anti-TB drugs
- Acts on all subpopulation – mainly slowly and intermittently dividing
- Both extra and intracellular organisms
- Sterilizing and resistance preventing

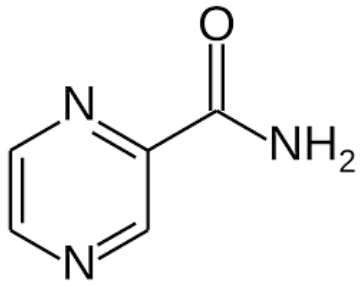
RIFAMPICIN – CONTD.

- **MOA:** Interrupts RNA synthesis
  - Binds to ß subunit of DNA-dependent RNA polymerase (*rboB*) – blocks polymerizing function
  - Human RNA polymerase ?
- **Resistance:** Primary resistance 1 in 10^{-7}
  - Developes rapidly and due to mutation of *rboB* gene – reduces affinity for drugs
  - Primary resistance – rare 2 %
  - No cross resistance
- **Kinetics:** well absorbed – 70% bioavailability – food interferes
  - Well distributed – penetrates intracellularly, cavities, caseous masees and placenta
  - Crosses meninges but pumped out – p-gp
  - Deacetylated in liver and excreted in bile and urine
  - Enterohepatic circulation
  - Half life 2-5 hours

RIFAMPICIN – CONTD.

- **Interactions:** Hepatic microsomal enzyme inducer – CYP3A4, CYP2D6, CYP1A2 and CYP2C
  - Induces own metabolism
  - Warfarin, OCPs, corticosteroids, sulfonylureas, protease inhibitors, NNRTIs, theophylline, metoprolol, fluconazole, clarithromycin, phenytoin, NNRTIs
  - Remember OCP - failure
- **Uses:** Leprosy, Meningococcal and H. influenzae meningitis, Brucellosis
- **ADRs:** Hepatitis – preexisting disease + >600 mg – jaundice discontinue
  - **Cutaneous syndrome:** flushing, pruritus, rash, redness and watering of eyes
  - **Flu syndrome:** chill, fever, headache, malaise and bone pain
  - **Abdominal syndrome:** nausea, vomiting, abdominal cramps – diarrhoea
  - Orange-red urine
  - Purpura, haemolysis, shock and renal failure

PYRAZINAMIDE (Z)



- Similar to INH – developed parallelly
- Weak bactericidal – more active in acidic medium – intracellular and inflammatory areas
- Highly active in first 2 months – kills residual intracellular bacilli – sterilizing
- Advantage: Shortening of duration of treatment and reduces risk of relapse
- **MOA:** Not clear – inside mycobacteria – active metabolite **pyrazinoic acid** by pyrzinamidase (*pncA*)
  - Accumulates in acidic medium and inhibits mycolic acid
  - Also disrupts cell membrane and transport
- **Resistance:** when used alone – mutation of *pncA* gene

PYRAZINAMIDE (Z) - CONTD.

- **Kinetics:** well absorbed orally, wide distribution, good CNS penetration (meningeal TB) – excreted in urine – half life 6 - 10 hours
- **ADRs:**Dose related hepatotoxicity – less among Indians (>30 mg/kg)
- Contraindicated in liver diseases
- Pregnancy?
- Hyperuricaemia – gout
- Abdominal distress, athralgia, flushing, rashes, fever, loss of diabetes control

ETHAMBUTOL

- Tuberculostatic – effective against MAC and some other fast multiplying bacilli
- With HRZ regimen – sputum conversion hastens and prevents resistance
- **MOA:** Not clear – inhibits arabinosyl transferase (embAB) involved in arabinogalactam synthesis – mycolic acid incorporation to cell wall prevented
- **Resistance:** slowly – mutation of embAB – no cross resistance to other drugs
- **Kinetics:** 3/4th of oral dose absorbed, low CNS penetration, stored in RBCs – excreted by gl. filtration – half life 4 hours
  - Renal diseases ?

ETHAMBUTOL – ADRS

- Good patient acceptability – low ADRs
- Loss of visual acuity/colour vision, field defects – due to optic neuritis
- Stop once visual defect occurs
- Children ?
- Early detected – reversible
- Contraindicated in optic neuritis
- Nausea, rash, fever, peripheral neuritis
- Pregnancy ?

STREPTOMYCIN

- First clinically useful anti-TB drug - aminoglycoside
- Tuberculocidal – less effective than INH or Rifampicin
- Only on extracellular bacilli – poor penetration
- Other drugs and host defence mechanism
- **MOA:** Inhibition of protein synthesis – binds to 30S and 50S subunits - freeze initiation and interferes polysome formation and misreading of mRNA code
- **Resistance:** rapidly and relapse – stop in resistance
    1. Acquiring of mebrane bound inactivating enzyme – phosphorylate/adenylate/acetylate the drug – conjugated drugs do not bind to target ribosomes - - - conjugation and plasmid mediated acquiring – nosocomial microbes
    2. Mutation decreasing the affinity of ribosomal proteins to drugs
    3. Decreased efficiency of transporting mechanism

STREPTOMYCIN - ADRS

- **Ototoxicity:** Most common – vestibular and cochlear damage – deposition in labyrinthine fluid – slowly removed – greater toxicity when persistent high plasma concentration
  - **Cochlear damage** – base to apex and high to low frequency sounds – no regeneration of sensory cells – permanent deafness
  - **Vestibular famage** – Headache – nausea, vomiting, dizziness, nystagmus, vertigo, ataxia
- **Nephrotoxicity:** Tubular damage – urinary conc. mechanism lost, low g.f.r., nitrogen retention, albuminuria and casts – due to deposition in cortex
- **Neuromuscular blockade:** reduce Ach

	Isoniazide	Rifamp	Pyrazin	Ethamb	Strepto
Nature	Cidal	Cidal	Cidal	Static	Cidal
Type of Bacilly	Both, fast multiplying	Both	intracellular	Both, fast multiplying	Basic
MOA	Mycolic acid	DNA dep RNA polymerase	Mycolic acid	Mycolic acid	Misreading of mRNA
Genes	InhA, KasA, KatG	rboB	pncA - pyrazinamidase	embA – arabinosyl transferase	-
Dose (mg/day)	5	10	25 - 30	15 - 20	15
***ADRs**	Peripheral neuritis, Hepatotoxicity, athralgia	Hepatotoxicity, Flu like, athralgia, urine colouration	Hepatotoxicity, Gout, athralgia	Visual acuity, hyperuricaemia	Ototoxicity, Nephrotoxicity
Points	Enzyme inhbition	Enzyme induction	Hepatotoxicity	Children	Low TI

*I (INH) practically (peripheral neuropathy) have (hepatotoxicity) right (Rifampicin) friends (flue like syndrome) or(orange-red discolouration) helpers (hepatotoxicity) providing (Pyrazinamide) help (hepatotoxicity generously (gout) & extremely visually hyperactive …..

FLUOROQUINOLONES

- Ofx, Lfx, Mfx and Cfx – bactericidal
- Active against – MAC, M fortuitum and other atypical ones
- Mfx > Lfx > Ofx > Cfx (But Cfx is most in atypical
- Penetrates cell and kill mycobacteria in macrophages
- **Uses:** Drug resistant TB (Lfx is standard in MDR TB)

OTHER DRUGS

- **Second line drugs:** Kanamycin Km), amikacin (Am), capreomycin (Cm)
  - Ethionamide (Eto), prothionamide (Pto), cycloserine (Cs), terizidone (Trd), PAS, rifabutin, rifapentine, bedaquilline

TREATMENT OF TUBERCULOSIS

BIOLOGY OF TUBERCULAR INFECTION

- Originally 18 – 24 months (1990) - but now 6 months short course
- Aerobic organism – unfavourable condition remain dormant or intermittently grow – several subpopulation
- **Rapidly growing with high bacillary load:** wall of a cavitary lesion (susceptible to H – less for R, E, S)
- **Slow growing:** located intracellularly and at inflamed sites (susceptible to Z – H, R and E are less active)
- **Spurters:** within caseous material – Oxygen tension is low and neutral pH (susceptible to R)
- **Dormant:** totally inactive for prolonged period – No anti-TB drug (Bedaquilline ?)

GOAL OF ANTITUBERCULAR THERAPY

- Kill dividing bacilli: sputum negativity, non-contagious and quick symptom relief
- Kill persisting bacilli: sterilize the patient and prevent relapse
- Prevent emergence of resistance: Bacilli remain susceptible to the drugs
- **Remember:** H and R are most potent bactericidal against all population
  - Z best on intracellular bacilli and those in inflamed sites and sterilizing activity
  - S is active against rapidly multiplying extracellular
  - E is bacteriostatic – prevent resistance and hsten sputum conversion

GENERAL PRINCIPLES

- Single drug – resistance and relapse 3/4th patients
- Combination of 2 or more drugs: Resistance naturally 10^{-8} to 10^{-6} - TB bacilli load in patient 10^{8} to 10^{10} high number of resistant bacilli - multiply and become dominant
  - But insensitivity is independent of that to another
  - Incidence of resistance to H among resistant to R will be 10^{-6} – only few bacilli and taken care by host defense – Bacilli load of $>10^{10}$ treated by 3 or more drug
- H and R are the most efficacious, synergistic (9-12 months)
- Addition of Z: reduces duration to 6 months
- A single daily dose of all first line drug – preferred (DOTS 1995)
- Fast response – symptomatic relief in 2 – 4 weeks

SHORT COURSE CHEMOTHERAPY

- WHO short course: 6 – 8 months multidrug short course regimens (DOTS) 1997 - Implemented in India (WHO)
- "Stop TB" strategy by WHO in 2006 – spread of MDR TB
- 2010 – New Case or previously treated or Drug resistant TB or MDR TB
- 2016 – WHO End TB strategy
- 2016 RNTP - Drug sensitivity test for DR-TB
  - Liquid culture and drug susceptibility test (L-DST) and genotyping tests for resistance to different drugs

TB TREATMENT

- **Intensive phase** 4 – 6 drugs: rapidly kill the bacilli and bring about sputum conversion (2 months)

- **Continuation phase** 3 – 4 drugs: to eliminate remaining bacilli (prevent relapse) – 4 months

TB CLASSIFICATION FOR DRUG REGIME

- **Drug-sensitive TB:** Sensitive to all 5 drugs – all new cases who have never taken any drug or taken for less than 1 (one) month
- **Multidrug resistant TB (MDR-TB):** Resistant to both **R** and **H** with or without resistant to any other drug
- **Rifampicin resistant TB (RR-TB):** Resistant to **R** but not to **H**, with or without resistant to other drugs – treated like MDR-TB
- **Mono-resistant TB:** Resistant to 1 (one) first line drug but not to **R**
- **Poly drug resistant TB** : Resistant to more than one first line drug but not to **R** and **H**
- **Extensive drug resistant TB (XDR-TB):** MDR-TB with resistance to 1 fluoroquinolone and 2nd line injectable drug

DRUG SENSITIVE TB

- New cases:
  - Initial 2 months: Treated with RHZ and E – reduces the risk of resistance – H
  - Next 4 months: After 2 months Z discontinued and continued with RHE (Old guideline E was not included and thrice weekly regime)
  - Given daily basis
- Previously treated:
  - Initial 2 months: Treated with SRHZ and E
  - 3rd month: No S but HRZE
  - Next 5 months: continued with RHE
- In severe extrapulmonary TB: P is extended by 3 – 6 months in both above cases
- Fixed dose combinations are recommended – patient takes all the drug + risk of bacilli being exposed to only 1 or 2 drugs

DRUG SENSITIVE TB

Table 56.1: Treatment regimens* for new patients and previously treated patients of pulmonary TB presumed to be drug sensitive

Type of patient	*Intensive phase*	*Continuation phase*	*Total duration*
New	2[£] HRZE	4 HRE	6 [£]
Previously treated	2 HRZES + 1 HRZE	5 HRE	8

* Based on RNTCP guidelines 2016.
[£] Duration of the phase/total duration in months.
H,R,Z,E,S—Standard codes for Isoniazid, Rifampin Pyrazinamide, Ethambutol, Streptomycin.

Table 56.2: Daily dose of 1st line antitubercular drugs on body weight basis[$]

Drug	*Daily dose (mg/kg)*
1. Isoniazid (H)	5 (4-6)
2. Rifampin (R)	10 (8-12)
3. Pyrazinamide (Z)	25 (20-30)
4. Ethambutol (E)	15 (15-20)
5. Streptomycin (S)*	15 (12-18)

[$] Based on WHO (2010) guidelines
* In patients above 50 years age, the maximum dose of streptomycin is 0.75 g/day

FDCS

Table 56.3: Daily dose of 1st line oral antitubercular drugs as number of fixed dose combination (FDC) tablets (based on RNTCP guidelines 2016)

Body weight category	*Intensive phase*	*Continuation phase*
	HRZE*	HRE$
25–39 kg	2	2
40–54 kg	3	3
55–69 kg	4	4
≥ 70 kg	5	5

* Intensive phase: each tablet contains H (75 mg) + R (150 mg) + Z (400 mg) + E (275 mg)

$ Continuation phase: each tablet contains H (75 mg) + R (150 mg) + E (275 mg).

MDR-TB

- Complex treatment – 3% of all new cases and 12 – 17% of retreatment cases – 2nd line drugs
- India highest number of MDR – 71000 cases annually
- 4 drugs at least certain to be effective or 6 drugs
- Depends on the DST results
- Avoid cross resistance drugs – 2 FQs, Km or Am, Eto with Pto or s with terizidone
- Standard RNTP 2016 – 6 drugs IPhase for 6 – 9 months and 4 drugs C phase for 18 months
- Include drugs from Gr. 1 to Gr. IV in hierachial order – Gr. I drug included (Z and E), 1 Gr.II drug, 1 Gr.III drug and 2 Gr.IV drugs
- Minimal 6 months I phase extended by 1 month each upto 9 months (sputum cultures in 4th, 5th, 6th months)

MDR - TB REGIME

Standard RNTCP regimen for MDR-TB*

Intensive phase	*Continuation phase*
(6–9 months)	*(18 months)*
1. Kanamycin (Km)	1. Levofloxacin
2. Levofloxacin (Lfx)	2. Ethionamide
3. Ethionamide (Eto)	3. Cycloserine
4. Cycloserine (Cs)	4. Ethambutol
5. Pyrazinamide (Z)	
6. Ethambutol (E)	

+ Pyridoxine 100 mg/day

*Revised National Tuberculosis Control Programme Guidelines (2016).

OTHER CASES

- **RR-TB:** treated like MDR-TB – **H** is added
  - IP 6 months with 7 drugs – Km, Lfx, Eto, S, Z, E, and H
  - 18 months continuation phase: Lfx, Eto, s, E and H

- **Monodrug resistant**: Resistant to 1 first line drug (DST or LPA (line probe assay): R + 2 of the first line drugs + I injectable 2nd line + 1 FQ daily in IP of 3 – 6 months (Total 9-12 months)

- **Poly drug resistance:** Resistance to more than 1 first line drug except R: R + 1 injectable 2nd line + 1 FQ + 1 first line drug + 1 oral 2nd line (Eto/Cs/PAS) – IP of 3 – 6 months – injectable stopped in CP (9-12 months)

- **Isoniazide resistant:** Low level due to mutation of *inhA* – dose increased upto 900 mg daily but in KatG mutation – does not work

XDR - TB

- Resistant to at least 4 effective drugs – H, R, FQ and one of Km/Am/Cm
- Difficult to treat
- Standard MDR-TB drugs must be stopped
- Cm 1000mg, Mfx 400 mg, H 900 mg, PAS 12 gm, Linezolid 200 mg, Amoxycillin/clavulanate 875+125 (2 tablets)
- IP 6 – 12 months and P 18 months

OTHERS

- Pregnancy and breast feeding – all standard drugs except Streptomycin
- Management of ADRs: anorexia, nausea – with small meals, drowsiness – bed time, athralgia – NSAIDS, Peripheral neuritis – Pyridoxin
  - Severe (skin rash, itching) stop and reintroduce one by one at low dose (R should not be reintroduced – haemolysis, thrombocytopenia etc.)
  - Optic neuritis – Ethambutol not to be reintroduced
  - Hepatotixicity: H, R, Z – stop till reaction subsides – start S and E - reintroduce one by one starting with R then Z – culprit drug should be stopped permanently

CHEMOPROPHYLAXIS

- To prevent from latent TB to active
- Contacts of open cases – recent Mantoux conversion
- Children with sputum positive in family
- Tubercular mother
- Leukaemia, diabetes, silicosis receiving immunosupressants
- HIV infected contacts of sputum positive cases
- 300 mg INH daily for 6 months
- INH high dose daily + Rifapentine once weekly – 3 months

CORTICOSTEROIDS AND TB

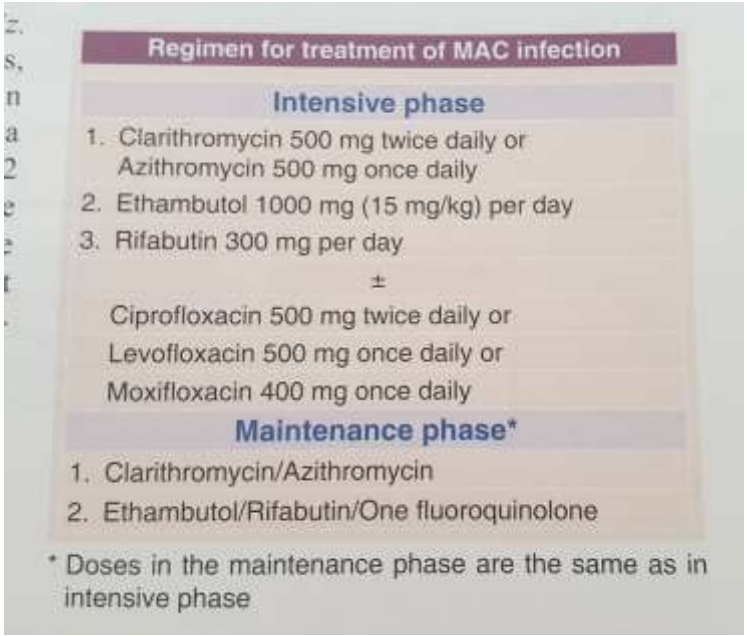
- Not given ordinarily
- Under adequate chemotherapeutic cover
- Seriously ill (miliary TB or severe pulmonary TB) – to buy time for anti TB to act
- Hypersensitivity reactions with anti TB drugs
- Renal/meningeal/pericardial TB or pleural effusion to prevent exudation
- In AIDS patients with severe menifestations of TB
- Contraindicated in intestinal TB

TB AND AIDS PATIENTS

- Serious problem – increases by 8 times
- Retroviral therapy and D4 cell count improvement reduces risk
- Treated like non-HIV patients – 2 months and 4 - 7 months (HRZE)
- Pyridoxine routinely 30 – 50 mg/day
- Cotrimoxazole to reduce mortality – Pneumocystis jiroveci
- Drug interactions – Rifabutin substitution for for R

MYCOBACTERIUM AVIUM COMPLEX (MAC)

- Opportunistic pathogen - Disseminated and multifocal disease in HIV-AIDS
- Eradication not achieved till now with any drug – suppress the disease only



Regimen for treatment of MAC infection

Intensive phase

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

±

Ciprofloxacin 500 mg twice daily or
Levofloxacin 500 mg once daily or
Moxifloxacin 400 mg once daily

Maintenance phase*

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

* Doses in the maintenance phase are the same as in intensive phase