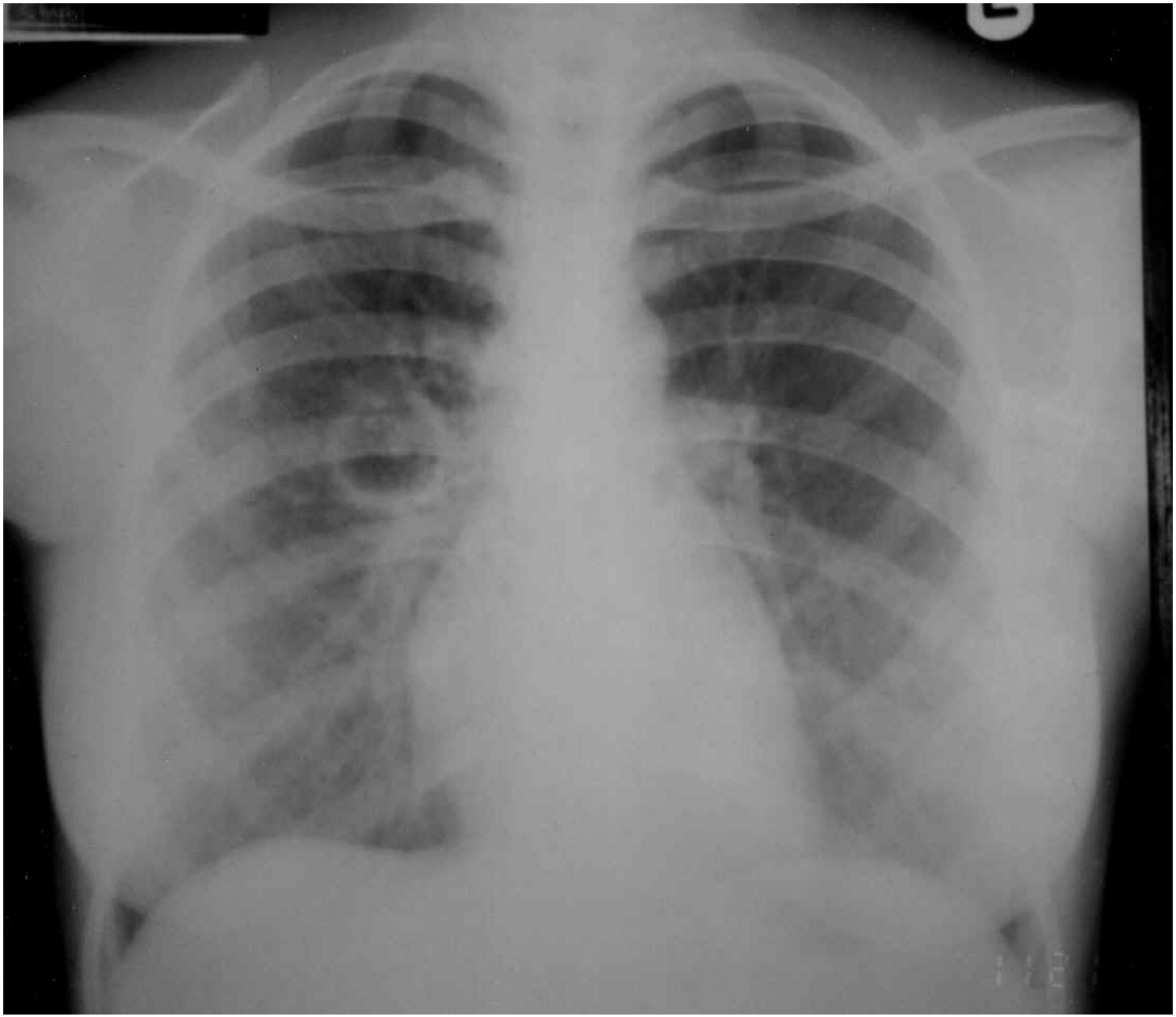
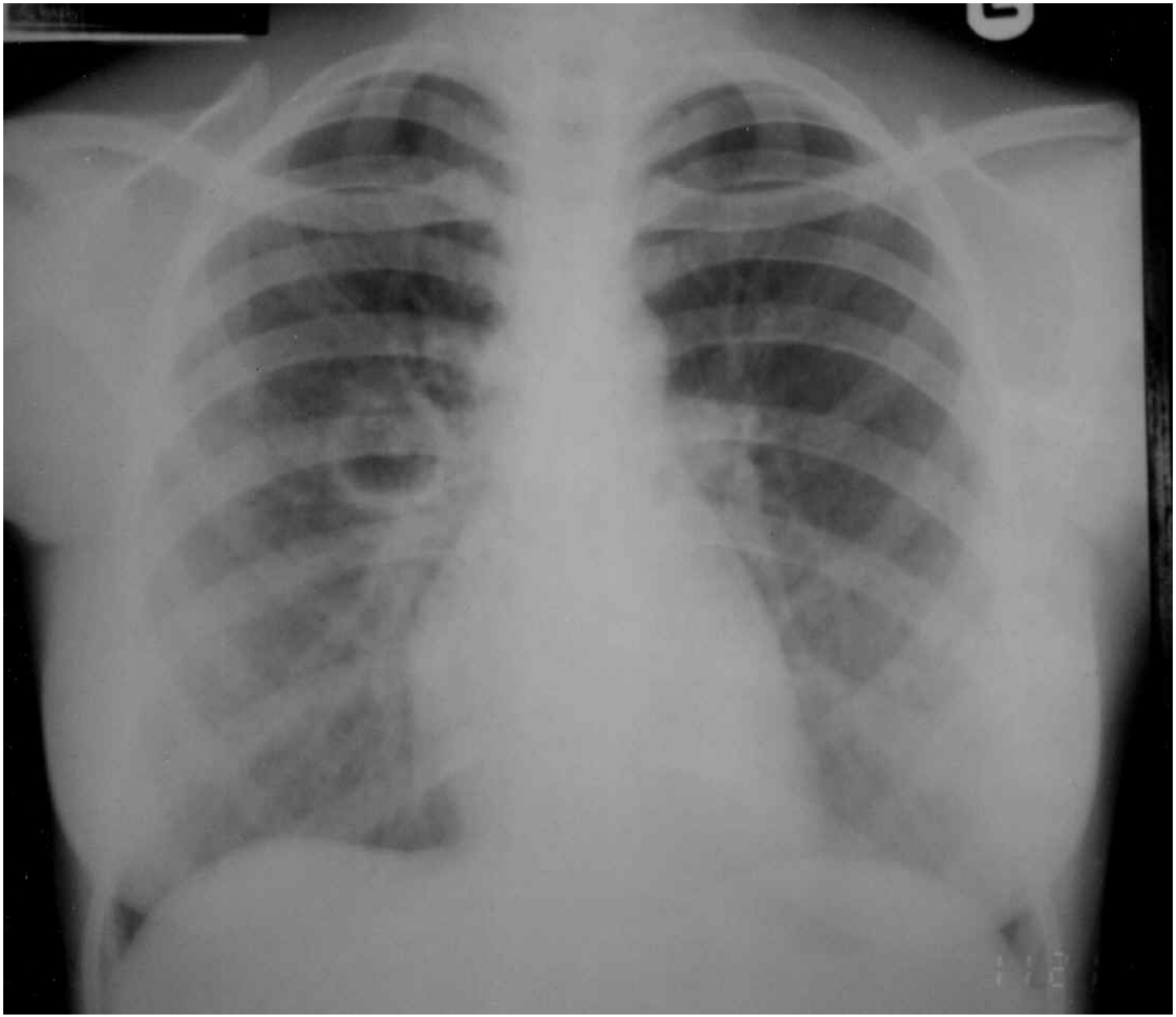
# CHEMOTHERAPY OF TB & LEPROSY



# INTRODUCTION

- History
- S/S
- Resistance
- Combination drug therapy
- High priority public health problem
- Very recently declared as a Notifiable disease in India



## Major Goals of TB Treatment

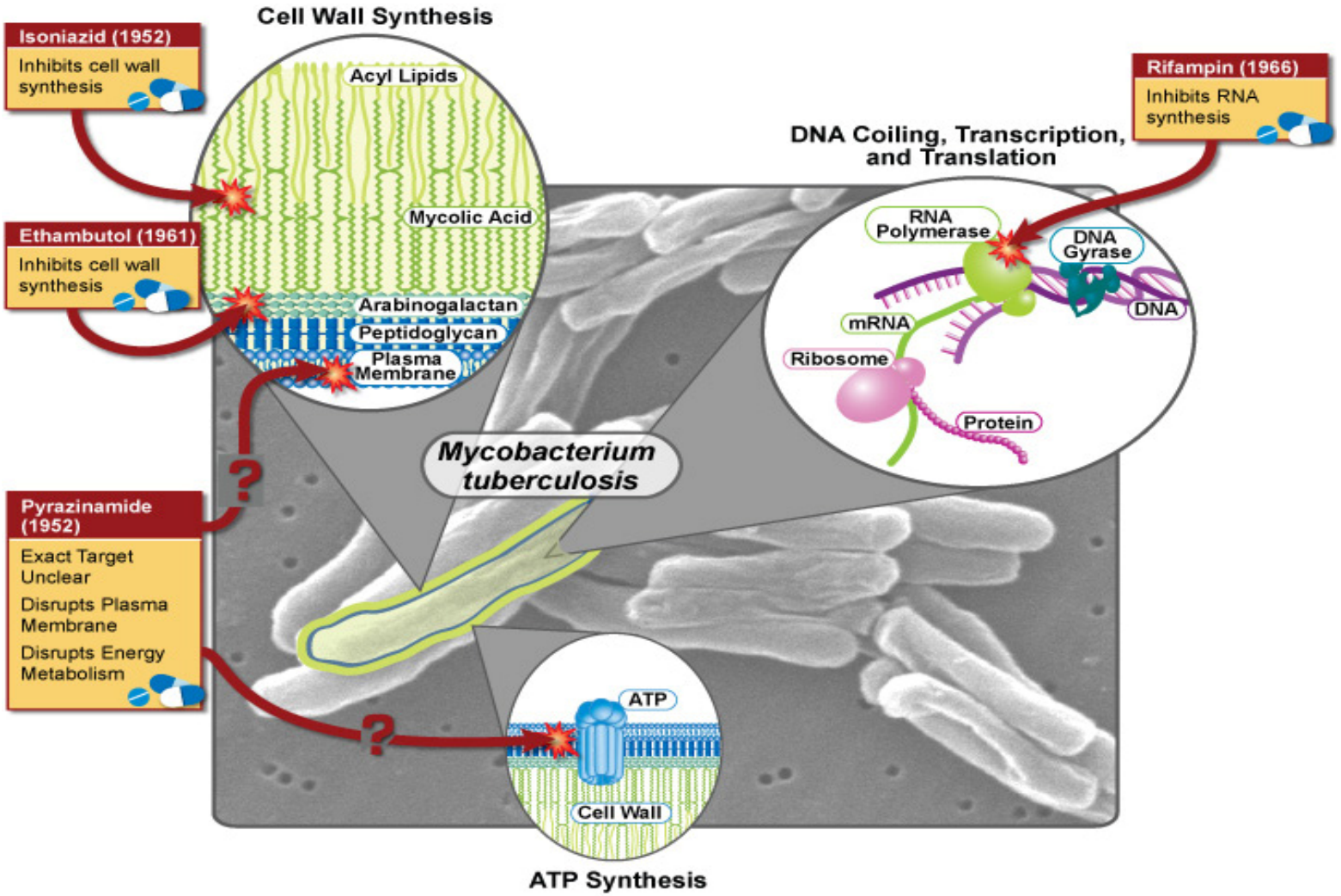
- Cure patient, minimize risk of death/disability, prevent transmission to others
- Provide safest, most effective therapy in shortest time
- Prescribe multiple drugs to which the organisms are susceptible
- Never treat with a single drug or add single drug to failing regimen
- Ensure adherence and completion of therapy

# CHEMOTHERAPY OF TB

- DRUG CLASSIF.
- First line – RHEZ,STM ,highly efficacious, acceptable limit of toxicity, used in combi 2-4 drugs to prevent resistance
- Second line – PAS, Ethionamide , cycloserine, clarithromycin, azithromycin, ciprofloxacin, ofloxacin,amikacin, …….. less effective, more toxic (except FQs).
- Usually TB therapy begins with 4 first line drugs RHEZ for 2 months followed by 2 drugs for 4 months on a daily basis or thrice with 4 first line drugs a week.

# Isoniazid

- INH : potent agent, str sim.to pyridoxine
- MOA Inhibits synth of mycolic acids (cell wall).INH is a prodrug activated by mycobact. Enz catalase peroxydase(kat G gene)
- Bactericidal to actively multiplying bacilli both EC + IC(in macrophages) & in acidic + basic medium
- Resist: Mutation of kat G gene/ mut. Of target gene inhA involv in myvolic acid synth
- PK: Well absb PO , Well distr. , no PPB, hepatic metab by NAT; genetic variation in rate of N-acetylation. Slow and fast acetylators , Toxicity


Cell Wall Synthesis
Isoniazid (1952)
Inhibits cell wall synthesis
Acyl Lipids
Mycolic Acid
Ethambutol (1961)
Inhibits cell wall synthesis
Arabinogalactan
Peptidoglycan
Plasma Membrane
Rifampin (1966)
Inhibits RNA synthesis
DNA Coiling, Transcription, and Translation
RNA Polymerase
DNA Gyrase
DNA
mRNA
Ribosome
Protein
Mycobacterium tuberculosis
Pyrazinamide (1952)
Exact Target Unclear
Disrupts Plasma Membrane
Disrupts Energy Metabolism
?
?
ATP
Cell Wall
ATP Synthesis

# INH(contd….)

- A/E :peripheral neuritis and hepatotixicity major dose dependent a/e
- Other a/e: allergic rxn, xerostomia, seizures, SLE
- DI: $AlOH_3$ ( antacids ) inhibits absb , PAS inhib metab, INH inhib metab of phenytoin, carbamazepine
- Dose Adult 300mg OD daily or 5mg /kg/day. If given thrice weekly : 10mg/kg/day or 600mg

# Rifampicin( Rifampin)

- A semisyn deriv of rifamycin. MOA: binds to bact DNA dep. RNA polymerase, inhibits RNA synth
- Bactericidal for IC & EC mycobact; also active agnst M leprae, Staph aureus, N meningitidis, H infl, Brucella, Chlamydia & legionella
- Has high sterilising & resist preventing act. Acts best on slowly mult bacilli
- Resist d/t point mut in rpoB gene
- PK: well absb PO, Penetrates all tiss, tubercular cavities, placenta and is highly PPB, excr mainly thru liver into bile .RMP - entrohepatic circul, deacetylated , Excreted in feces

# RMP(contd…)

- Potent enz inducer
- In combi with other 1st line drugs used for trt. of all forms of pulm & extra pulm TB.
- Dose 600mg/day or 10mg /kg/day single dose BB . OR 600mg single dose thrice weekly
- Other indic: leprosy, prophylaxis of meningococcal & H infl meningitis & carrier state, MRSA inf. , legionella, brucellosis (with doxy)
- A/E Major - Hepatitis , dose dep & reversible, rash, gi , dizziness , "flu –like synd", red orange colour urine
- DI cyp450 induction- increases metab of OCP , anticoag, protease inhib

# Ethambutol

- Synth. tuberculostatic ,
- Active agnst M tubercolosis, M kansasi & M avium intracellulare.
- MOA- inhibits arabinosyl transferase enz- prevents polymeriz. of arabinoglycans in cell wall. Resistance d/t pt mut. In Emb B gene –encodes AT enzyme
- PK : Well absb PO , widely distributed , majority excr. unchanged(85% ) in urine.
- Dose 800-1000 mg PO (15mg/kg/day) or 1600mg/day(30mg/kg/day) thrice a week.
- Also used in combi with clarithromycin and rifabutin in trt of MAC in AIDS pt

- A/E : can cuase optic neuritis: ↓vis acuity & loss of red-green color vision; dose & durn  dep.(in pt using 25mg/kg/d for >9 mths; 15% pt on 50mg/kg) , slowly reversible, periodic visual acuity test be done
- avoid in children <5 yr,
- Other A/E ; rash, fever, gi, jnt pain, ↓urate exc. ---ppt.gout

# Pyrazinamide(PZA)

- Pyrazine deriv of nicotinamide, converted to pyrazinoic acid by bact pyrazinamidase enz
- MOA: inhibits mycolic acid synth, active at acidic pH, highly effective on i/c mycobact, Bcidal,.
  Resist d/t mut in pcnA gene
- PK : well abs PO , widely dist. in tiss, macro, tubercular cavities & meninges. Exc primarily by kidneys.
- Dose 1500mg (25mg/kg/day) or 2000mg(35mg/kg/day) thrice a week
- A/E: Major: Hepatotoxicity- monitor LFT , hyperuricemia, n ,v, anorexia, drug fever.

# Streptomycin

- 1st drug to exhibit. effective action on Myco
- Exerts action only on extracell. bacilli: less effective
- Dose ;adults 15mg/kg/day in 2 dd, max 1gm/day,
- Nephro and ototoxicity- reserve 1st line drug

# Rifabutin

- Str anal of RMP, Common MOA, spectrum of acn, & mol basis of resistance
- Difference: Less potent enz inducer: lesser drug interac.; better act agnst MAC, longer t1/2
- PK : well absb PO , widely distr.,hepatic metab, exc thru kidney
- Used in place of RMP in TB in HIV inf pt & for prevention & trt of MAC in HIV pt.Dose 300mg/d
- A/E :skin rash, GI, hepatitis , neutropenia
- **Rifapentene** : also RMP anal, common MOA, resist, enz induc, A/E & cl.use, NOT used alone

# 2nd Line drugs

- **Ethionamide**
- Bacteriostatic agent,
- Well absb PO ,rapidly & widely distr  incl CSF, extensively metab in liver
- Used only as 2nd line, given orally as 250mg BID initial dose to a max 1gm /day
- A/E :Intense GI irit. ,metallic taste, postural hypotension, depression, asthenia, convulsions , allergic rxn, hepatitis
- Monitor LFT, give concom. pyridoxine

# PAS

- Bstatic agent, str analog of PABA (like sulphonamides): inhib folate synth of mycobacteria only
- Readily absb in git, distributed exten. except CSF, metab in liver (acetylation), 80% excr thru kidneys- CI in CRF
- Dose 10-12 g orally daily in 2-4 dd, gastric irritant , used rarely
- A/E :git intolerance- poor compliance, hypersensit rxn, jnt pain , malaise, fever, skin erupt, leukopenia, agranulocyt, Ac hem anemia

# Cycloserine

- Broad spectrum ,inhibits bact cell wall synth
- Tuberculostatic, also active agnst E coli,staph, enterococcus,nocardia, chlamydia
- Readily absb PO, widely distr. incl CSF, mainly excreted unchanged by kidney, CI in renal insuff
- Dose 250-500mg BID
- A/E : CNS mainly :H,V, tremor, dysarthria,vertigo, conf, irritability, psychotic state with suicidal tendencies, seizures: CI in epilepsy

# Thiacetazone

- Tuberculostatic, well absb PO , excreted mainly unchanged in urine,
- Dose 150  mg OD
- Once 1st line ,now used only in special cases d/t A/E like ototoxicity & life threatening hypersensitivity rxns: hepatitis , BMD, neutropenia, skin rash, GI intolerence & drug fever.

# Other second line drugs( injectable)

- **Capreomycin** :Tuberculocidal polypeptide AMA
- Effective agnst M.tuber, M.kansasi, M.avium
- Poorly absb PO : given parenterally 1g/day IM
- A/E sim to AGs
- Imp drug for MDR TB
- **Kanamycin & Amikacin**
- AGs: Kana obsolete, Amikacin used for MDR TB & MAC in AIDS pt: 15mg/kg/day IM/IV
- A/E: nephro, ototoxicity

# FQs & Macrolides

- FQs : imp recent addition esp for MDR strains, also effective as part of regimen in HIV inf pt
- Cipro , Oflox, Spar, levo, Moxi inhibit 90-95% of strains of suscept Myco incl MAC & M.fortuitum
- PK : good intacellular penetrating capacity, convenient dosage schd. Good tolerability
- Cipro 750 mg BID or 500mg TDS, Oflox 400mg BD, Levo 500mg OD, Spar 400mg OD, Moxi 400mg OD , all PO
- **Macrolides :** Clarithromycin 500mg BID PO, & Azithro 500mg OD.V active agnst M kansasii, M fortuitum, M marinum & MAC. Limited act agnst M tuber.Useful for prevention & treatment of MAC in AIDS pts
- Newer drugs : linezolid,

| Category & type of patient (DOTS)RNTCP | Duration of treatment | Drug regimen |
|---|---|---|
| Category I<br>•New (untreated ) smear +ve pulmonary TB<br>•New (untreated) smear –ve pul. TB, but seriously ill<br>•New cases of seriously ill extrapul TB | For all such cases<br>Intensive phase -2 mths followed by Continuation phase- 4 months<br>Total 6 months | RHEZ<br>RH |
| Category II<br>Smear +ve retreatment gpd/t<br>•Treatment failure<br>•Default /relapse | For all cases<br>Intensive phase 2+1=3 mths<br>Contin. Ph.5 mths<br>Total 8 mths | RHEZS2mth<br>RHEZ 1mth<br>RHE |
| Category III<br>•New smear –ve pul.TB not seriously ill<br>•Less severe cases of E-Pul TB | For all cases<br>Intensive phase 2mths<br>Continuation phase4 mths Total 6 mths | RHZ<br>RH |

- MDR TB: "TB that is resistant to H & R ". 2nd line drugs are used for longer duration. DOTS Plus used to manage MDR as CAT 4 .More difficult to treat.
- XDR TB: " MDR TB that is also resistant to any FQ & to one of the three inj 2nd line drugs ( kana, amika , capreo). treatment v. difficult , takes 18-24 mths of 4-6 2 nd line drugs.

# Treatment of MDR TB (DOTS PLUS)

- Preferably the standardized regimen as recommended in the national DOTS-Plus guidelines should be used [6(9) Km Ofx Eto Cs Z E / 18 Ofx Eto Cs E] †
- If results of 2nd line DST from an accredited laboratory are available, an individualized regimen may be used in such patients after obtaining a detailed history of previous anti-TB treatment

# MDR TB-Duration of treatment

- At least six months of Intensive Phase (IP) should be given, extended up to 9 months in patients who have a positive culture result taken at 4th month of treatment
- Minimum 18 months of Continuation Phase (CP) should be given following the Intensive Phase

# Treatment of TB…..

- Chemoprophylaxis: H 300mg/day:6-12mths ;RZ:2 mths effective in HIV ipt
- Pregnancy & breastfeeding: RHZ safe, E in last trimester only. Full course to nursing mother but give infant H prophylaxis
- Corticosteroids in TB: gen avoided, CI in intest TB, Indications:

# Treatment of MAC

- TB inf in HIV more severe. Drug regimen same as for CAT1 pt but continuation phase last 7 mths ie total durn is 9 mths
- MAC inf common in HIV pts , causes disseminated ds in later stage of AIDS:Common regimens are :
- Clarithromycin 500mg BID + E 15mg/kg/d Azithro 500mg OD + E 15mg/kg/d Azithro 500mg OD + E 15mg/kg/d+ Cipro750 mg BID or Rifabutin 300mg OD

# Drug treatment of leprosy (Hansen's Disease)

- Intro :
- Since 4000 BC
- Written Records in ancient Egyptian papyrus in 1500 BC
- For categorizing patients for chemotherapy:
- The disease was well recognized in ancient China, Egypt, and India, and there are several references to the disease in the religious texts.

Because of Hansen's discovery of *M. leprae*, efforts were made to find treatments that would stop or eliminate*M. leprae*; in the early 1900s to about 1940, oil from Chaulmoogra nuts was used with questionable efficacy by injecting it into patients' skin. At Carville in 1941, promin, a sulfone drug, showed efficacy but required many painful injections. Dapsone pills were found to be effective in the 1950s, but soon (1960s-1970s), *M. leprae* developed resistance to dapsone. Fortunately, drug trials on the island of Malta in the 1970s showed that a three-drug combination (dapsone, rifampicin [Rifadin], and clofazimine [Lamprene]) was very effective in killing *M. leprae*. This multi-drug treatment (MDT) was recommended by the WHO in 1981 and remains, with minor changes, the therapy of choice. MDT, however, does not alter the damage done to an individual by *M. leprae* before MDT is started.

- 1) **Paucibacillary leprosy** : non-infectious with few bacilli , mainly tuberculoid type:
- <5 hypoesthetic skin lesions, more neural involvement
- Normal or partially def. CMI. T-cells produce interferon γ, enable macrophages to kill i/c M.leprae
- Bacilli rarely found in biopsies
- Lepromin test +
- Prolonged remissions with periodic exacerbations

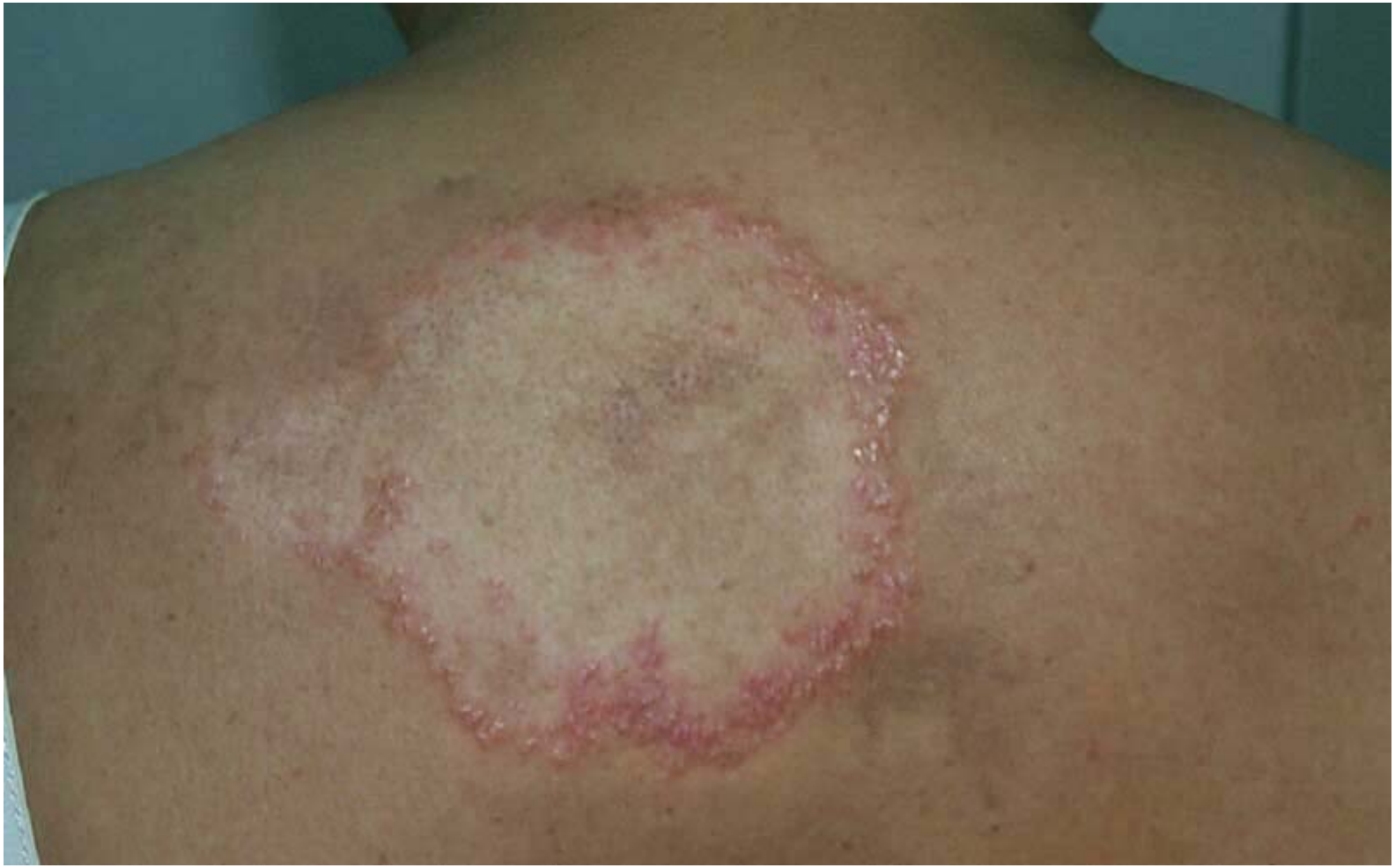
- **Multibacillary leprosy** : infectious with numerous bacilli. Mainly lepromatous type of leprosy
- >5 hypoesthetic ,diffused skin lesions with MM infiltration
- CMI largely deficient , I-response mainly by IL-4 ,block axn of IF- γ
- Skin & MM numerous bacilli
- Lepromin test –ve
- Ds later progresses to anaesthesia of distal parts & wounds

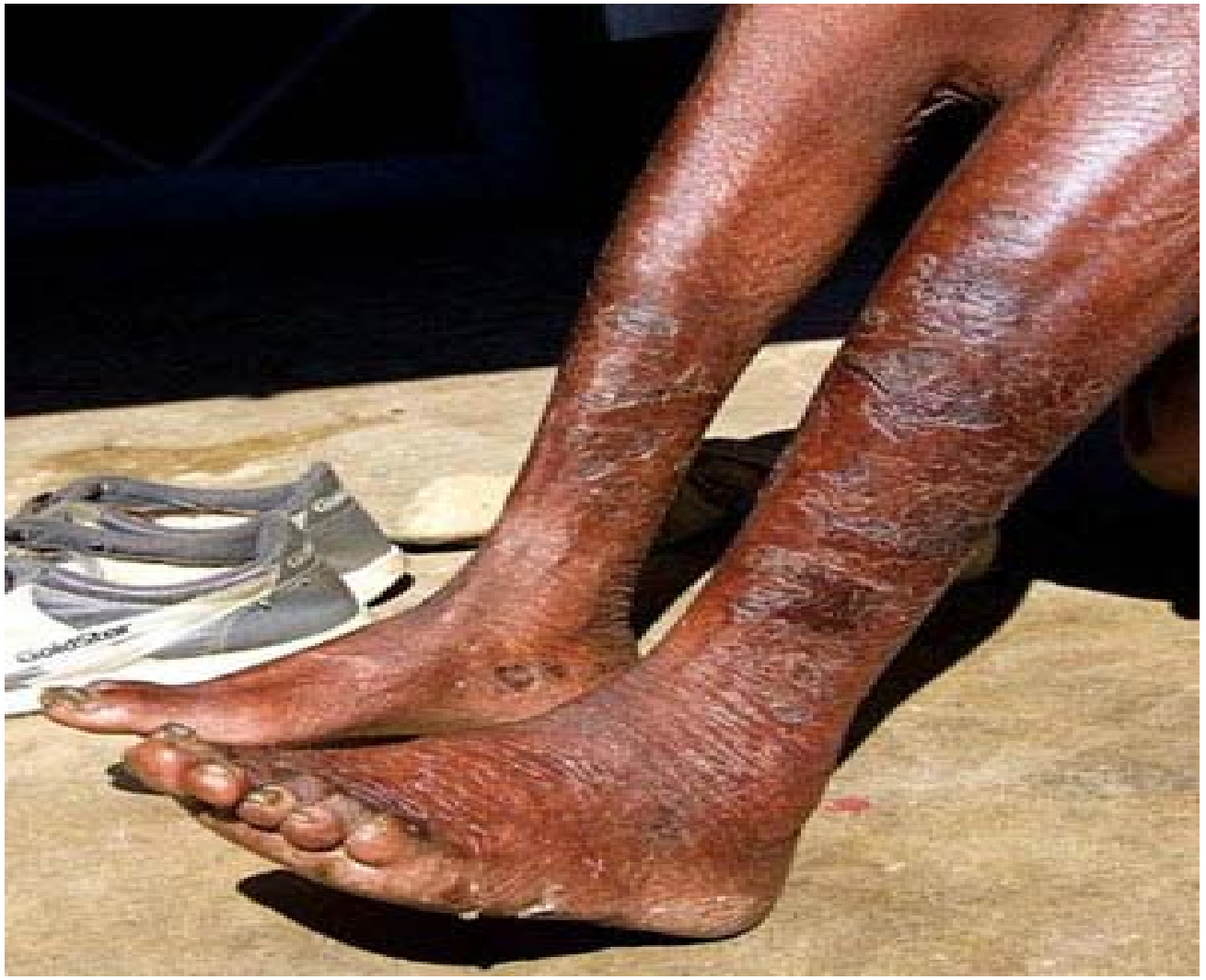
## Table 1

### Classification of Leprosy

| Classification | | Description | | | | | |
|---|---|---|---|---|---|---|---|
| WHO | Ridley-Jopling | Number of lesions | Margins of lesions | Surface | Sensation | Nerve Involvement | Skin Smear |
| Paucibacillary (single-lesion or 2 to 5 lesions; tuberculoid) | Indeterminate (I) | One or few, hypopigmented | Poorly defined | Smooth | Diminished | — | Negative |
| | Tuberculoid (TT) | Single, infiltrated patch | Well defined | Dry, scaly | Absent | Variable | Negative |
| | Borderline tuberculoid (BT) | Few to multiple, varying size | Well defined | — | Diminished to absent | Variable | Negative to 1+ |
| Multibacillary (> 5 lesions; lepromatous) | Mid-borderline (BB) | Multiple, macular-papular, plaque-like | Variable, asymmetric distribution | Shiny to dry and scaly | Diminished | Peripheral nerve enlargement | Few to moderate bacilli |
| | Borderline lepromatous (BL) | Multiple, macular-papular, nodular | Poorly defined, symmetric distribution | Smooth and shiny | Diminished or absent | Peripheral nerve enlargement | Many bacilli |
| | Lepromatous (LL) | Multiple, macular-papular, nodular | Poorly defined, symmetric distribution | Smooth and shiny | Absent from dorsal portions of distal extremities | Enlargement found later | Highly positive |

*Adapted from references 4, 5, and 18.*





# Drug treatment of Leprosy

Drugs for leprosy:

- Sulphones: **Dapsone (Diamino diphenyl sulfone, DDS)**, Acedapsone ( prodrug, IM depot inj -long acting)
- Phenazines : **Clofazimine**
- ATT : **RMP**
- AMAs : FQs ( Oflox, Sparflox), Macrolides (Clarithro), Tetras( Minocycline)

# Dapsone (DDS)

- Closely related to sulphonamides, inhibit bact folate synth, leprostatic
- Resistance develops if used alone hence combined with R & clofazimine
- Dose 100mg/day PO .Also useful for prophylaxis & trt. Of PCP & dermatitis herpetiformis
- Well abs PO ,widely dist, esp. concentrated in skin ,ms & kidney upto 3 wks after stopping therapy . Acetylated in liver, entero hepatic circ. Metabolites & some unchanged drug are excreted via urine. Pl. T1/2 1-2 days.

- **Dapsone (contd…)**
- Resistance: m/b primary or sec.
- **A/E** : usually well tolerated , but may cause hemolytic anemia & methemoglobinemia in pts with G6PD def.
- Other A/E Nausea, anorexia, pruritus, drug fever , reversible neuropathy and hepatotoxity
- During therapy for Leprosy reactive episodes may occur: **lepra rxns**. 2 types :**Type I lepra rxn** or **reversal rxn**: delayed HS rxn to M.leprae Ag (TypeIV)- cut. Ulceration & multiple nerve involv. Us. occur during trt of TL. CS are used.

# Dapsone (contd….)

- **Type 2 lepra rxn** or erythema nodosum leprosum **(ENL**). Seen in LL , are humoral Ab response (Type III) to dead bact. Abrupt onset, existing lesions enlarge, , become red, inflamed & painful, fever. Clofazimine or CS or ***Thalidomide*** used. **Sulfone syndrome**' develops 5-6 wks after initiation of trt in malnourished pt- fever , malaise , jaundice & hepatic necrosis, LAP, anemia, methhemo

# Clofazimine

- Phenazine dye binds pref to myco DNA, interferes with its template fnct & inhibits growth. Leprostatic with anti-inflamm properties- useful in lepra rxn
- Used for Dapsone resist leprosy or in dapsone intolerant pt. Dose 100mg/day PO, lag pd of 6-7 wks
- Oral abs variable, elim thru feces, t1/2 60-70 hrs, widely distr incl phagocytes
- A/E :Reddish brown discolouration of skin, eosinophilic enteritis, others-phototoxicity & conjunct discolor. , avoided in preg,

# Rifampicin

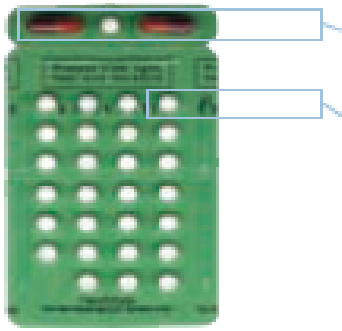
- Bcidal to M.leprae,rapidly kills 99.9% bact in 5-6 days , but used in combi as resist develops after prolonged trt. Usual dose in LL 600mg once a month
- **Ofloxacin**(400mg/d) & **Sparfloxacin** used as alternative drugs
- **Clarithromycin** - only macrolide with antileprotic act. Dose 500mg/d ,usedan alternative drug
- **Minocycline** –only tetra with antileprotic act. Can be used as 100mg/d as substitute to clofazimine in std regimen

# WHO regimen for leprosy trt

- For Multibacillary leprosy (LL): **Dapsone** 100mg/d+ **Clofazimine** 50mg/d together with 300mg once a month(29+1 days) + **RMP** 600mg once a month for 12 **months** ,under supervision
- For Paucibacillary leprosy (TL): **Dapsone** 100mg/d + **RMP** 600mg once a month for **6** months .If dapsone not tolerated then Clofazimine 50mg /d & 300mg once a month
- **Alter regimen for** Multibacilary L :if RMP is unsuitable (Resistance/intolerance) : **Clofazimine** 50mg/d+**Oflox** 400mg/d+ **Minocycline**100mg/day for first **6 mths** ,then **Clofaz** 50mg/d+ **Oflox** 400mg/d (or Mino 100mg/d) for further **18 mths**

# MDT Regimens

Each blister pack contains treatment for 4 weeks.



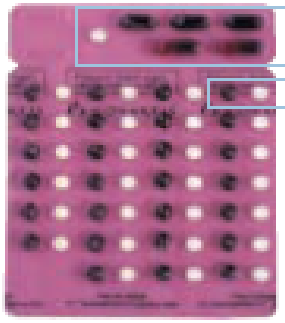
PB adult blister pack

**PB adult treatment:**

**Once a month:** Day 1
– 2 capsules of rifampicin (300 mg X 2)
– 1 tablet of dapsone (100 mg)

**Once a day:** Days 2–28
– 1 tablet of dapsone (100 mg)

**Full course:** 6 blister packs



MB adult blister pack

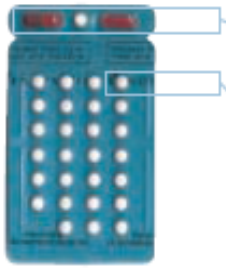
**MB adult treatment:**

**Once a month:** Day 1
– 2 capsules of rifampicin (300 mg X 2)
– 3 capsules of clofazimine (100mg X 3)
– 1 tablet of dapsone (100 mg)

**Once a day:** Days 2–28
– 1 capsule of clofazimine (50 mg)
– 1 tablet of dapsone (100 mg)

**Full course:** 12 blister packs

**It is crucial that patients understand which drugs they have to take once a month and which every day.**



PB child blister pack

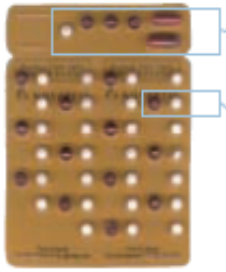
### PB child treatment (10–14 years):

**Once a month:** Day 1
– 2 capsules of rifampicin (300 mg+150 mg)
– 1 tablet of dapsone (50 mg)

**Once a day:** Days 2–28
– 1 tablet of dapsone (50 mg)

**Full course:** 6 blister packs

For children younger than 10, the dose must be adjusted according to body weight.



MB child blister pack

### MB child treatment (10–14 years):

**Once a month:** Day 1
– 2 capsules of rifampicin (300 mg+150 mg)
– 3 capsules of clofazimine (50 mg X 3)
– 1 tablet of dapsone (50 mg)

**Once a day:** Days 2–28
– 1 capsule of clofazimine every other day (50 mg)
– 1 tablet of dapsone (50 mg)

**Full course:** 12 blister packs

For children younger than 10, the dose must be adjusted according to body weight.