Tuberculosis

Tuberculosis

- Mycobacterium tuberculosis
- Mainly affects the lungs (80% of cases), 10-15% of cases- other organs. Miliary TB
- Transmission - inhalation of infected droplet nuclei
- HIV –TB
- S/S
- Curable
- Main problems in treatment are
    - Noncompliance
    - Drug toxicity
    - Resistance
    - AIDS

Antitubercular drugs

First line drugs

Bacteriostatic	Bactericidal
Ethambutol (E)	Isoniazid (H)
	Rifampicin (R)
	Pyrazinamide(Z)
	Streptomycin (S)

Second line drugs

Bacteriostatic	Bactericidal
Cycloserine	
Terizidone	Amikacin
PAS	Kanamycin
Thiacetazone	Capreomycin
Ethionamide Prothionamide	
Linezolid	Ciprofloxacin
	Ofloxacin
	Levofloxacin Moxifloxacin
	Bedaquiline
	Delamide

According to efficacy and priority in use

Group 1 First-line oral anti-TB drugs

Isoniazid (H)
Rifampicin (R)
Ethambutol (E)
Pyrazinamide (Z)

Group 2 Injectable anti-TB drugs (injectable or parenteral agents)

Streptomycin (S)
Kanamycin (Km)
Amikacin (Am)
Capreomycin (Cm)

Group 3 Fluoroquinolones (FQs)

Levofloxacin (Lfx)
Moxifloxacin (Mfx)
Ofloxacin (Ofx)

- **Group 4 Oral second-line anti-TB drugs**

  Ethionamide (Eto)
  Prothionamide (Pto)
  Cycloserine (Cs)
  Terizidone (Trd)
  p-Aminosalicylic acid (PAS)

- **Group 5 Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB**

  Bedaquiline (Bdq)
  Delamanid (Dlm)
  Linezolid (Lzd)
  Clofazimine (Cfz)
  Amoxicillin/clavulanate (Amx/Clv)
  Imipenem/cilastatin (Ipm/Cln)
  Meropenem (Mpm)
  Thiacetazone (T)
  Clarithromycin (Clr)

Isoniazid (Isonicotinic acid hydrazide) INH

Cheap, effective, less toxic

Treatment and prophylaxis

Effective against –

1) Extracellular bacilli (Rapidly growing in wall of cavitary lesion)

2) Intracellular bacilli (Slow growing in macrophages)

3) Not effective against persisters.

Mechanism of action

Bactericidal

It is a prodrug

Enters mycobacteria-converted by catalase peroxidase enzyme to a reactive metabolite-inhibit InhA and KasA gene involved in mycolic acid synthesis

It inhibits synthesis of mycolic acid-important constituent of cell wall of mycobacterium tuberculosis

Resistance-mutation in catalase-peroxidase

Pharmacokinetics

- Orally absorbed
- Metabolized in liver –Acetylation
- Hepatotoxic minor metabolite- CYP2E1
- Pharmacogenetics

Slow acetylators-Indians

Fast acetylators-Twice weekly regimen not effective

Acetylator status not so important when taken daily

Adverse effects

1.Peripheral neuritis

A]It inhibits pyridoxine kinase which converts pyridoxine to pyridoxal phosphate-in synthesis of NT, amino acids

B]Reacts with pyridoxal to form hydrazones-increase excretion of pyridoxine

- **Paresthesias**
- **Numbness**
- **Burning pain along the distribution of sensory nerves**
- **More in Slow acetylators**

To prevent it – pyridoxine – 10 mg/ day-Routine use not mandatory-as uncommon with therapeutic dose

MUST in- alcoholics, pregnancy, diabetes, HIV

2.Hepatitis

- **? Fast acetylators – more prone**
- **Alcoholics -more prone- induces CYP2E1**
- **acetyhydrazine-toxic metabolite –Hepatic necrosis**
- **Rare in children**
- **More common in Indians**
- **Reversible**

3. Dizziness, psychotic behavior Convulsions

DI- PAS inhibits INH metabolism

Rifampicin

Expensive

Effective against :-

1) **Extracellular bacilli**

2) **Intracellular bacilli**

3) **Highly effective against persisters – multiplying in caseous material**

High sterilizing effect

Mechanism of action

- **Bactericidal**
- **Inhibit DNA dependent RNA polymerase – inhibiting RNA synthesis**

Pharmacokinetics

- **Good oral absorption**
- **Food interferes with absorption**
- **Before breakfast**

Metabolized in liver – Active metabolite

- **Enterohepatic circulation**
- **Enzyme inducer. DI-contraceptive failure/protease inhibitors, NNRTIs**

Adverse effects

1. Orange –red discoloration of all secretions
2. Hepatitis –Reversible
3. Nausea, vomiting
4. flu like syndrome

Other uses

1) Prophylaxis of meningococcal and H. influenzae meningitis20mg/kg/day for 4 days
2) Meningococcal and H. influenzae carriers -600mgBD-2days
3) Brucellosis-with doxycycline-600+200mg/day-6wks
4) Leprosy
5) Pneumococcal meningitis-resistant to penicillin
6) MRSA-Osteomyelitis

Pyrazinamide

Inexpensive

Mainly active against intracellular bacilli

More active in acidic medium-inflammation

Only in intensive phase

Effective against persisters

Sterilizing effect ++

Mechanism of action

- **Bactericidal**
- **Not known**
- **converted inside the bacterial cell to pyrazinoic acid by pyrazinamidase**
- **Accumulates in acidic medium-inhibit mycolic aid synthesis**

Pharmacokinetics

- Good CSF Concentration –useful in TB meningitis
- Metabolized in Liver

Adverse effects

1. Hepatotoxicity –With 25-30mg/kg-low incidence, less common in Indians
2. Hyperuricemia – Inhibit secretion of uric acid- may precipitate gout
3. Arthralgia-common

Streptomycin

- Aminoglycoside
- Only effective against extracellular bacilli
- Cidal drug
- Less effective

Labeled as a 'supplemental' first line drug

Use limited d/t

1) Parenteral administration
2) Ototoxicity, Nephrotoxicity
3) Resistance-S-dependence

Ethambutol

Effective against

1) **Intracellular bacilli**
2) **Extra cellular bacilli**
3) **Also effective in MAC infection**

Mechanism of action

Bacetriostatic

Exactly not known

Inhibit arabinosyl transferase-inhibit arabinoglycan synthesis

Inhibits mycolic acid incorporation in cell wall.

Less effective

It prevents emergence of resistant strains of M. tuberculosis

Adverse effects

Optic neuritis

- **Decreased visual acuity**
- **Decreased ability to differentiate between red and green colour**
- **Visual symptoms precede a measurable decreased acuity**
- **Reversible after stopping the drug**
- **Use in children with due precaution**

50% of drug excreted in urine

Ethambutol has replaced PAS, thiacetazone

- **Better acceptance**
- **Less toxicity**

Second line drugs

Para- amino salicylic acid (PAS)

Least active, inhibits folate synthase

Delays development of resistance

Patient acceptability poor – Large dose-10-12g/day

- Anorexia, nausea

For MDR TB-if other static drugs or cidal drug-Km Ofx, Z,Eto can't be used

Thiacetazone

Stevens – Johnson syndrome, Hepatitis

Cycloserine

- Tuberculostatic ,MAC
- Inhibits cell wall synthesis
- Excreted unchanged by kidney-renal tuberculosis
- Causes peripheral neuropathy and CNS dysfunction –Pyridoxine

Terizidone

2 molecules of cycloserine, less neurotoxic

Toxic reactions-rarely observed

Ethionamide –inhibits mycolic acid synthesis

- **MAC**
- **Gastric intolerance** **Rarely used**
- **Neurologic symptoms**

Prothionamide

Better tolerated

Kanamycin, Amikacin

Ototoxicity, Nephrotoxicity

Parenteral administration

S-resistant, MDR TB

Amikacin-less toxic.15mg/kg-5days a week-2months,1g/day thrice a week

RFTs, audiometry

Capreomycin

Alternative to aminoglycoside

Fluroquinolones

- Well tolerated among second line drugs
- Active against MAC infection
- Moxifloxacin-most effective
- Ciprofloxacin-no more used
- Levofloxacin replaced ofloxacin due to resistance
- Effective against extracellular, intracellular bacilli
- Convenient dosage schedule

- **Bedaquiline**
- belonging to the diarylquinoline class of antibiotics , selectively targets mycobacterial ATP synthase, and enzyme essential for supply of energy to mycobacterium leading to inadequate ATP synthesis, which is necessary for bacterial metabolism
- Strong bactericidal and sterilizing activities against MTB
- It has no cross-resistance with first- and second-line ATD
- Bedaquiline and its metabolites-long half life-present in plasma 5-6 months after stopping
- The results of two trials (phase II) suggested that a standard 2-month treatment regimen with bedaquiline yielded high culture conversion rates, rapid sputum culture conversion and low acquired resistance to companion drugs in newly diagnosed MDR-TB cases

- 400 mg daily for 2 weeks, then 200 mg three times a week for 22 weeks with food, added to OBR (as per WHO recommendations) to treat MDR-TB in adults with other three anti TB drugs –sensitivity testing+
- when the following conditions are met: Pharmacovigilance is in place, informed consent is ensured and QT monitoring is possible
- RNTCP introducing BDQ at six sites in the country initially
- Basic criterion – Adult aged ≥18 years having pulmonary MDR TB
- Female should not be pregnant./ using non-hormonal contraceptive
- Written informed consent from patients
- Initial 2 weeks treatment-indoor, after discharge treatment will be continued on ambulatory basis with strict adherence and follow up

- Delamanid
- cell walll synthesis inhibitor
- By poisoning them with nitric oxide, which the drugs release when metabolized
- 100 mg film-coated table BD -24 weeks

- Linezolid,
- a first-generation oxazolidinone, demonstrated clinical effectiveness in most difficult-to-treat drug-resistant cases,
- although the frequency and severity of adverse events (*i.e.* peripheral neuropathy, optic neuropathy, gastrointestinal disorders and myelosuppression) limit its long-term use
- 600mg OD, normal course BD-Less side effects
- proper treatment drug monitoring (TDM) approach

Second line drugs

1. Low efficacy
2. High cost
3. High toxicity
4. Low sterilizing effect

Use – Patients intolerant to 1st line drugs

Resistant to 1st line drugs-MDR TB

Conventional regimen

Duration of treatment -12-18 months

Short course chemotherapy-DOTS

Advantages

1. **Duration of Treatment less – 6-9 months**
2. **Less cost**
3. **Less defaulter rate**
4. **Negligible relapse rate**
5. **Less toxicity**

In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and **daily dosing remains the recommended dosing frequency**

patients who received **thrice-weekly dosing had a higher risk of treatment failure, disease relapse and acquired drug resistance** in both drug-susceptible disease and when the strain susceptibility was unknown.

If thrice-weekly dosing during the continuation phase is used, it is essential to make sure that patients do not miss any dose of medications and that DOT is used. In

Aims of treatment

1. **Control active TB – control s/s**
2. **Make patient non- infectious – sterilize**
3. **Prevent complications, relapse**
4. **Prevention of drug resistance**

Tuberculosis Pulmonary

Extra pulmonary

Anti tubercular drugs are always used in combination

1. **Duration of treatment reduced**
2. **Prevention of development of resistance**
3. **Rapid decrease in bacterial load**

Intensive phase

2.3 months

Rapid decrease in bacterial load

Continuation phase

4-6 months

Eliminate remaining bacilli –To prevent relapse

Drug	Daily dose(mg/kg)
Isoniazid (H)	5
Rifampicin (R)	10
Pyrazinamide (Z)	25
Ethambutol (E)	15
Streptomycin	15

-fixed dose combination as daily doses

WHO guidelines for treatment of tuberculosis

Category I

- **New cases of pulmonary and extra pulmonary tuberculosis**

  2(HRZE) + 4(HRE)

Category II

Recurrent TB case (Relapse), Treatment after failure (Treatment failure), Treatment after loss to follow-up(defaulter)

Intensive phase -2(HRZES) + 1(HRZE)

Continuation phase – 5 (HRE)

30 days of previous anti-TB treatment being the cut-off

Drug susceptibility testing (DST) (rapid and/or conventional) is strongly recommended by WHO in all cases and particularly for those previously treated

New case – A TB patient who has never had treatment for TB or has taken ATD for <1 month. (*No change in new guidelines*.)

- Previously treated patients have received one month or more ATD in the past. This may be:
  - Recurrent TB case – A TB patient previously declared as successfully treated (cured/treatment completed) and who is subsequently found to be microbiologically confirmed TB case (*Previously called relapse*.)
  - Treatment after failure – Patients are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

- Treatment after loss to follow-up – A TB patient previously treated for TB for one month or more and who was declared lost to follow-up in their most recent course of treatment and subsequently found microbiologically confirmed TB cases.

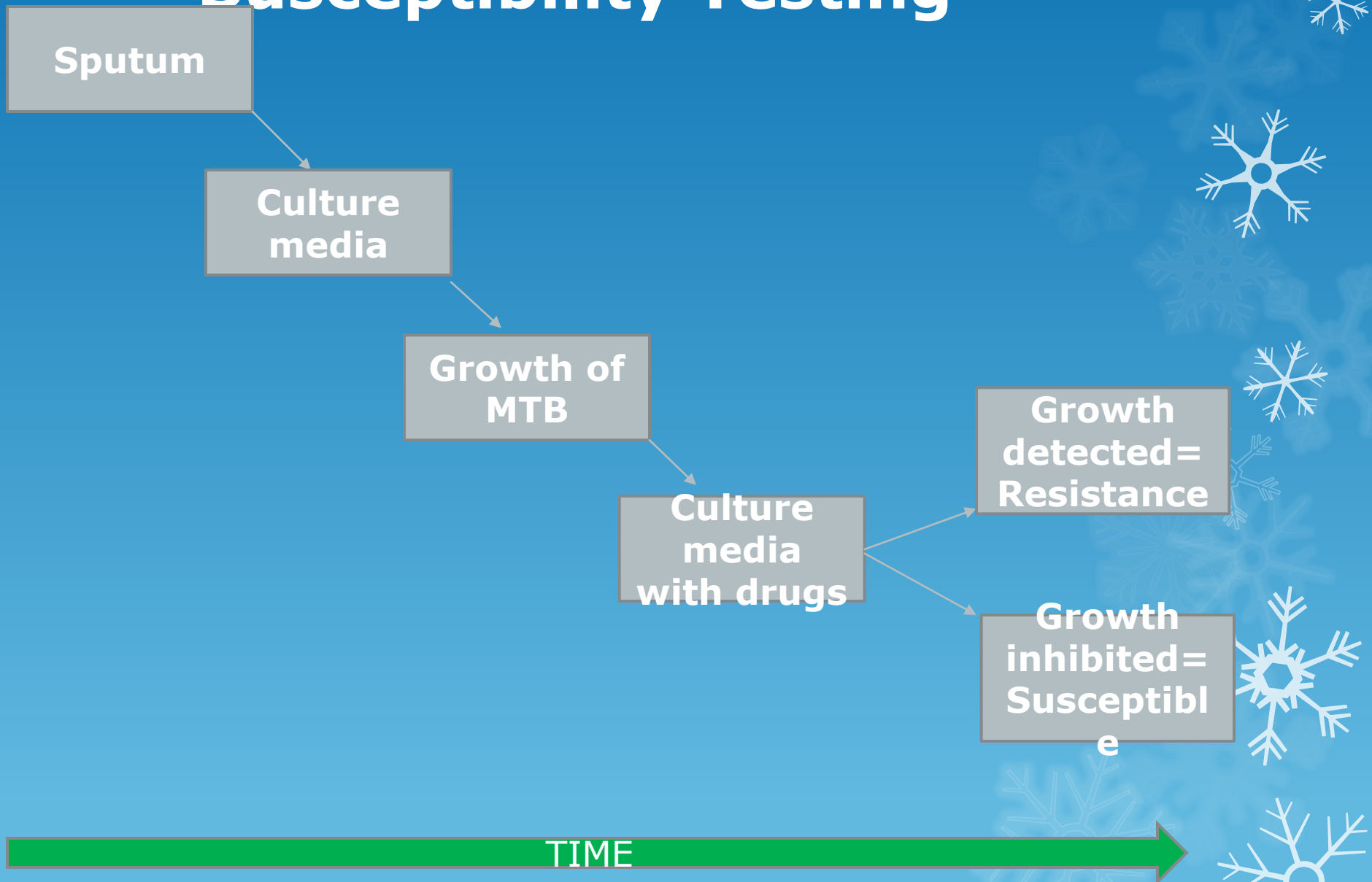
Previously called treatment after default – a patient who has received treatment for TB for a month or more from any source and return for treatment after having defaulted, that is, not taking ATD consecutively for 2 months or more and found to have smear-positive.

New guidelines	Previous guidelines
Daily regimen	Intermittent regimen
Ethambutol in CP of both categories I and II regimen	Ethambutol in CP of category II regimen only
Fixed dose combination as per weight band	No fixed dose, limited weight band
No need of extension of IP	Extension of IP for 1 month if sputum is positive at the end of IP
Follow-up-clinical, laboratory investigation	Follow-up-laboratory only
Long-term follow-up up to 2 years	No long-term follow-up

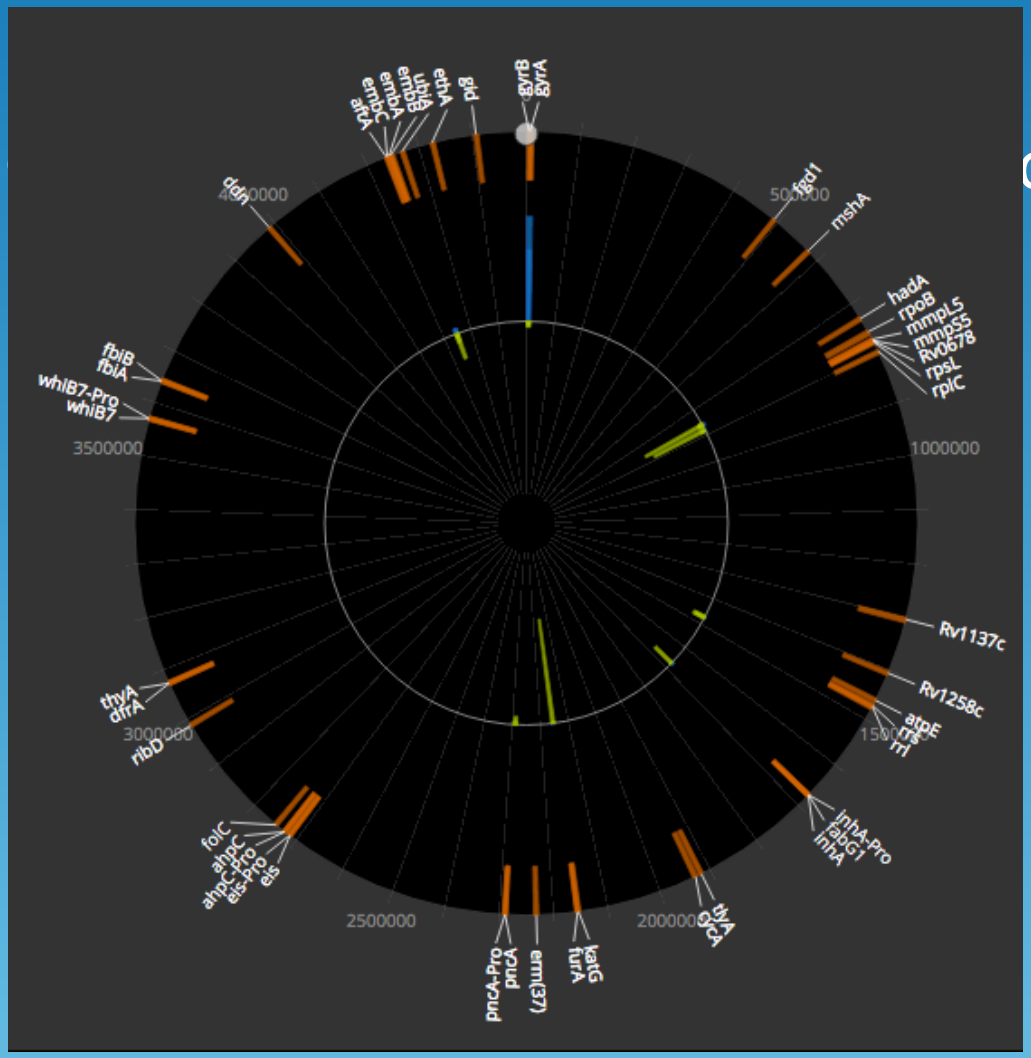
- Drug sensitivity testing-must before starting the treatment
- Liquid culture, drug susceptibility test
- Line probe assay-faster genotype test-for R and H resistance
- Cartridge based nucleic acid amplification test for R resistance

- Patient weight wise 4 band ,boxes containing full course of treatment and packaged in blister packs. In each patient wise box there are two pouches. One is for the intensive phase and the other is for the continuation phase.
- Red-New, Blue-previously treated

Phenotypic Drug Susceptibility Testing



Molecular Detection of Drug Resistance



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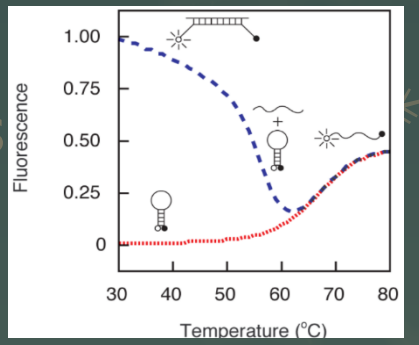
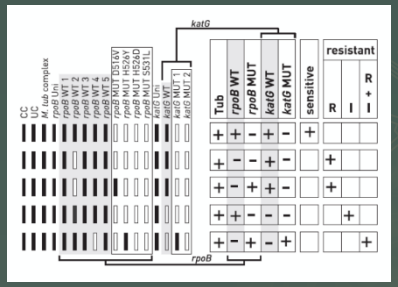
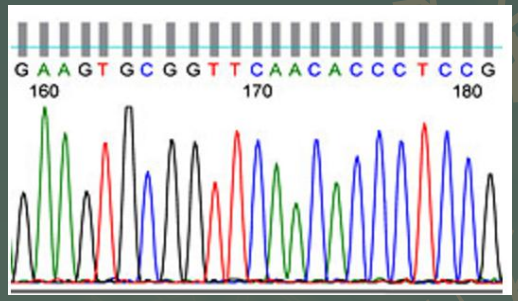
1. MOLECULAR BEACON ASSAYS



2. LINE PROBE ASSAYS

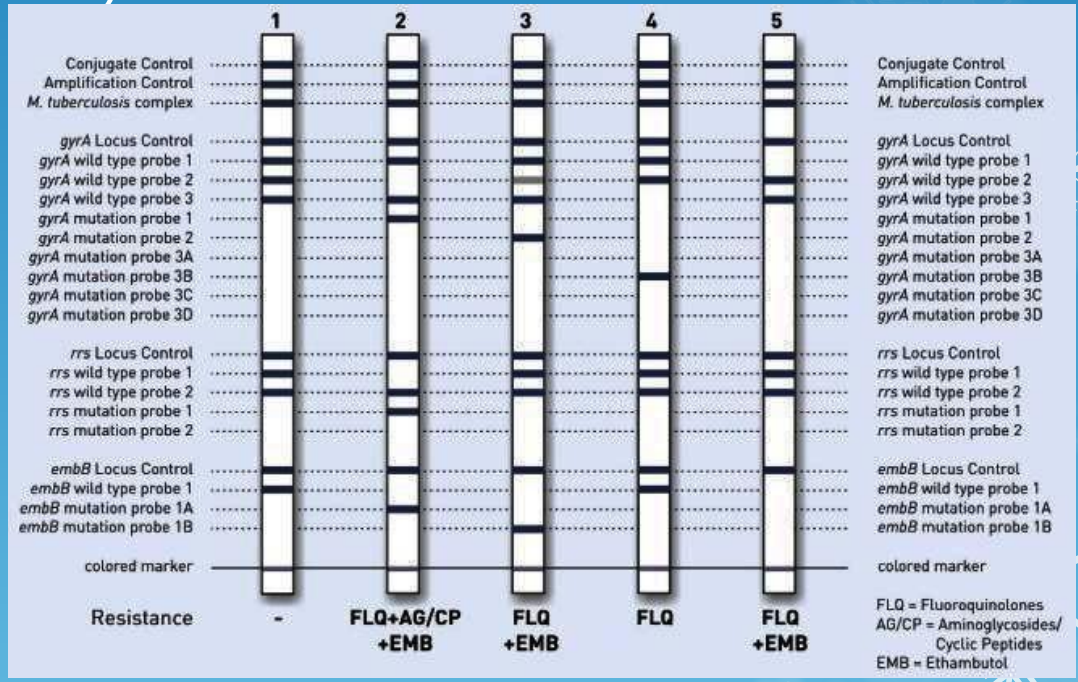


3. SEQUENCING



Second line molecular drug resistance testing

- Genotype®MTBDR*sl* (MTBDR*sl*): commercially available
  - Detects resistance to key second line drugs:
  - Fluoroquinolones(FQ): ofloxacin, moxifloxacin, levofloxacin
  - Second Line Injectable Drugs (SLID, amikacin, kanamycin, capreomycin)
- Performance (pooled results)
  - FQ:
    - Sensitivity 83%
    - Specificity 98%
  - SLID
    - Sensitivity 77%
    - Specificity 99.5%



Source: Theron et al. Cochrane 2014

Weight category	Number of tablets (FDCs)		Inj. Streptomycin
	Intensive phase HRZE 75/150/400/275	Continuation phase HRE 75/150/275	gm
25-39 kg	2	2	0.5
40-54 kg	3	3	0.75
55-69 kg	4	4	1
>=70	5	5	1

- Fixed dose combinations of ATDs –

  Patient takes all the drugs

  Bacilli exposed to all the drugs

  Resistance-low

Pill burden reduced *as instead of seven tablets, patients need consume only 2 or 3 tablets, according to their weight band*

Each patient will receive through the RNTCP a month's supply of drugs.

- E in continuation phase-high chance of H resistance

- **Follow-up of treatment:**
  Clinical follow-up

  Should be at least monthly – the patient may visit the clinical facility, or the medical officer may conduct the review when she/he visits the house of the patient to observe improvement of chest symptoms, weight gain, control the co-morbid conditions such as HIV and diabetes and to monitor any adverse reaction to ATD.

[

- ***Follow-up laboratory investigation***

  For PTB cases – sputum smear examination at the end of IP and at the end of treatment. (In the previous guidelines, follow-up sputum smear to be done at 2, 4 and 6 months for new cases and 3, 5 and 8 months in previously treated cases.)

  In case of clinical deterioration, the Medical Office may consider repeat sputum smear even during CP. (New addition.)

- At the completion of treatment, sputum smear and culture should be done for every patient.
- CXR – to be offered whenever required and available.

- *Long-term follow-up*

  After completion of treatment, the patient should be followed up at the end of 6, 12, 18 and 24 months. Any clinical symptoms and/or cough, sputum microscopy and/or culture should be considered. (New addition) However, there was no provision of long-term follow-up *in the previous guidelines*.

Pregnancy

- **I, R, E,Z– Safe**
- **S – Contraindicated**

2HRZE plus 7HRE

Pyridoxine 10-25mg/day

Lactating mother

All are safe

Infant-BCG Vaccination and 6 month Isoniazid

Jaundice occurs during the treatment

- Stop
- INH
- Rifampicin
- Pyrazinamide

Streptomycin, Ethambutol continue

After LFTs normal-drugs are restated one at a time

R is resumed first followed 7 days later by H

- Extrapulmonary TB-new or previously treated
- CP may be extended by 12-24 weeks
- Extension beyond 12weeks only on recommendation by expert

Multidrug resistant TB

India has Highest number of MDR TB patients

Resistance to both H and R positive with or without resistance to other anti-tubercular drugs based on drug susceptibility test results from an accredited laboratory.

Not a clinical diagnosis-sputum culture and sensitivity

Lack of properly organized system to ensure effective treatment

Treatment complex, second line drugs, Long term treatment

Regimen for MDR TB

2 group I drugs+1 group II-injectable+1 FQ + 2 group IV

Intensive phase-6-9 months

Km+Lfx+Eto+Cs+Z+E

Continuation phase-18 months

Lfx+Eto+Cs +E

Pyridoxine 100 mg/day to all patients during whole course of therapy

Although DST-guided individualized regimens have to be preferred,-for levofloxacin and kanamycin standardized regimens are used in setting where DST is not available.

The treatment of MDR/XDR-TB is unfortunately long, toxic and expensive, and the success rate largely unsatisfactory

Drugs to be taken

DOTS

DOTS Plus

- Extensively drug resistant TB
- MDR TB CASE RESISTANT TO FQS AS WELL AS TO ONE OF THE INJECTABLE SECOND LINE DRUGS from a RNTCP-certified Laboratory. Culture & DST
- Difficult to treat
- High mortality
- Thiacetazone, Clarithromycin, Clofazimine, Linezolid, Amoxicillin/Clavulanate
- Drugs with unclear efficacy

- IP-6-12ms

  Cm+PAS+Mfx+High dose H+Cfz+Lzd+Amx-Clav
- CP-18 ms

  PAS+Mfx+High dose H+Cfz+Lzd+Amx-Clav

  Daily treatment under supervision

Tubercular meningitis

- Duration of treatment more. continuation phase to be extended by 3 months
- Usually 5 drugs are combined in intensive phase
- Use of glucocorticoids

Use of gulcocorticoids in treatment of TB

- Given as an adjuvant in treatment of TB
- No direct action against mycobacterium tuberculosis
- Always given with adequate anti –TB drugs

Aim

- To decease active inflammation
- To decrease subsequent fibrosis
- Used in situation – Fibrosis, Scarring-deterious effect

Indications of glucocorticoids in patients suffering from tuberculosis

1. Tubercular meningitis
   - Enhance absorption of exudates
   - Prevent formation of adhesions
   - Decrease toxemia

2 Tuberculosis of serous membranes – pleura, pericardium ,Large pleural effusion ,TB pericarditis

3 Endotracheal Tuberculosis

4 Ocular tuberculosis

5 Addison's disease

6 Genitourinary tuberculosis

Prednisolone – 60-80 mg/day –Taper over 4-6 wks.

TB + HIV

- Serious problem
- Higher incidence of extra pulmonary TB
- More severe, More infectious
- A/E more common with anti TB treatment
- HRZE for 2months+HRE for 6-9 months
- Rifabutin can be substituted for Rifampicin as less drug interactions
- Pyridoxine

Chemoprophylaxis

Prevention of setting in of an infection or suppressing contacted infection before it becomes clinically manifest

INH –10 mg/day

Primary prophylaxis

- **Prevent implantation bacilli**
- **Household contacts**
- **Neonate of tubercular mother**
- **TT-negative**
- **Duration-6months**

- **Secondary prophylaxis**
- **Prevent development of a disease after infection has occurred**
- **TT- +ve**
- **Duration 1 year**

- **INH resistance-combination of H[5mg/kg]+R[10mg/kg]-3months**

Mycobacterium avium complex infection

- In Immunocompromized patients
- In HIV patients
- Intensive phase-Macrolide +Ethambutol +Rifabutin +Quinolone
- Continuation phase- Macrolide+ Ethambutol/Rifabutin/Quinolone
- Chemopropylaxis- Macrolide or Rifabutin

- *As per the previous guidelines, a pulmonary TB suspect was defined as*:

  An individual having cough for 2 weeks or more
- Contacts of smear-positive TB patients having cough for any duration
- Suspected/confirmed extra-pulmonary TB having cough for any duration
- HIV-positive patient having cough for any duration.
-

  But according to the new guidelines –

  Presumptive pulmonary TB refers to a person with any of the symptoms or signs suggestive of TB:

  cough >2 weeks,
- fever >2 weeks,
- significant weight loss,
- haemoptysis,
- any abnormalities in chest radiography.
- WHO has recently launched its innovative "End TB Strategy" [1], supporting the TB elimination strategy and the vision of a TB-free world with zero death, disease and suffering due to TB
-

Newly developed drugs

Delamanid, Bedaquiline and Pretomanid

Repurposed drugs

Linezolid

Meropenem +Clavulanate,

- **Meropenem/clavulanate**
- Meropenem +clavulanate is active *in vitro* against *M. tuberculosis*, showing a good tolerability profile.
- Meropenem and clavulanate together have a potent *in vitro* activity against *M. tuberculosis*, as clavulanate inhibits the extended-spectrum β-lactamase (BlaC) produced by TB bacilli, which generally hamper the activity of β-lactam antibiotics like meropenem.

- **sutezolid**
- Sutezolid (PNU-100480), like linezolid (see section on repurposed drugs), belongs to the oxazolidinone class of antibiotics. Their mechanism of action prevents the initiation of protein synthesis by binding to 23S RNA in the 50S ribosomal subunit of bacteria.
- **SQ109**
- SQ109, a 1,2-ethylenediamine, is an analogue of ethambutol. The drug is active against both drug-susceptible and drug-resistant TB by targeting MmpL3 in *M. tuberculosis* and specifically inhibiting the protein synthesis [61]. *In vitro*, it has some synergic effects with bedaquiline and favourable interactions with sutezolid. SQ109 is presently undergoing phase II clinical trials (table 6) [48].
- **Benzothiazinones**
- This new class of anti-TB drugs, in the pre-clinical development phase, are able to inhibit the synthesis of decaprenylphosphoarabinose, the precursor of the arabinans in the mycobacterial cell wall