Antitubercular Drug

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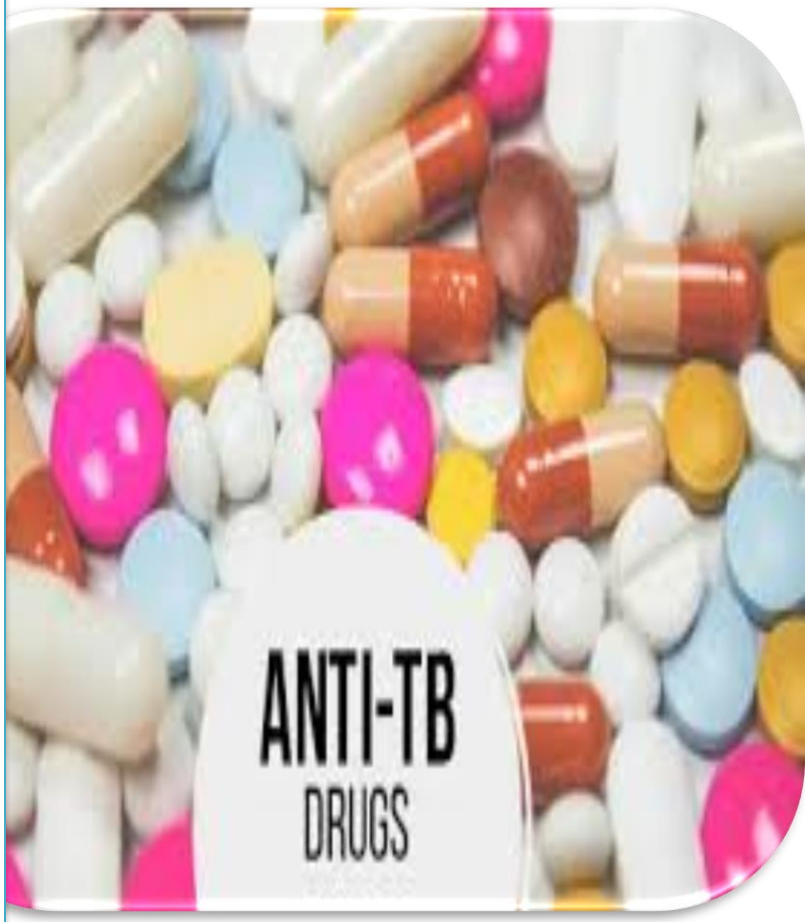


Introduction

- **What is Tuberculosis?**
- **Tuberculodsis (TB)** is an **airborne infectious disease** caused predominantly by **Mycobacterium tuberculosis** species of pathogenic bacteria, first discovered in **1882 by Robert Koch.**
- Tuberculosis typically **attacks the lungs** but can also affect other parts of the body.

- **Characteristics of Mycobacterium tuberculosis bacillus –**
- These are fairly large ,facultative ,intracellular,non motile ,& rod shaped bacterium that are 2-4 microns in length & 0.2-0.4 microns in width .
- It is an obligate aerobe that's why MTB complexes always found in the well aerated upper lobes of the lungs .

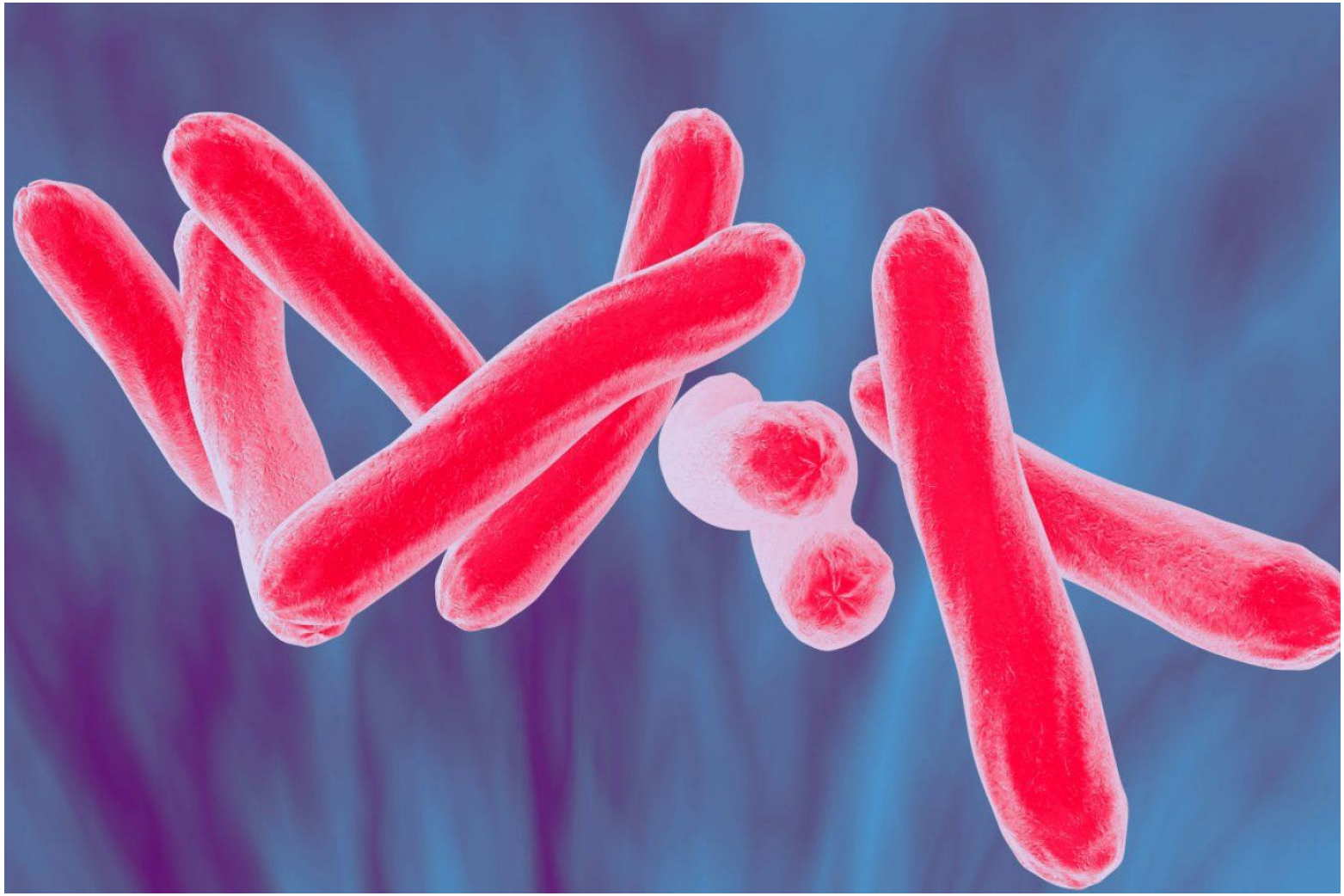


Fig : Mycobacterium tuberculosis

- **Classification of TB.**
- **TB cases (bacteriologically confirmed or clinically diagnosed) are classified according to the:**
- 1. Anatomical site of disease
- 2. History of previous treatment
- 3. Drug resistance
- 4. HIV status

Classification of TB

- **Classification based on Anatomical site of disease:**
- i. Pulmonary TB (PTB)
- Ii. Extrapulmonary TB(EP TB)

- **Classification based on History of previous TB treatment:**
- i. New
- Ii. Previously treated

- **New:** A patient who has never taken treatment for TB or a patient who has taken Anti-TB drugs for less than one month.

- **Previously treated:** A patient who has received Anti-TB drugs for one month or more in the past.

- **Based on the outcome of their most recent course of treatment, previously treated TB are sub-classified as:**
- i. Relapse
- ii.Treatment after failure
- iii.Treatment after loss to follow up
- iv. Other previously treated

- Relapse: in this case pts have been treated previously for TB ,were declared cure or treatment completd at the end of their most recent course of treatment and are now diagnosed with a recurrent episode of TB.
- Treatment after failure : in this pts have been treated previously for TB and whose treatment failed at the end of their most recent course of treatment.

- Treatment after loss to follow up:in this pts have been treated previously for TB and were declared lost to follow up at the end of their most recent course of treatment.

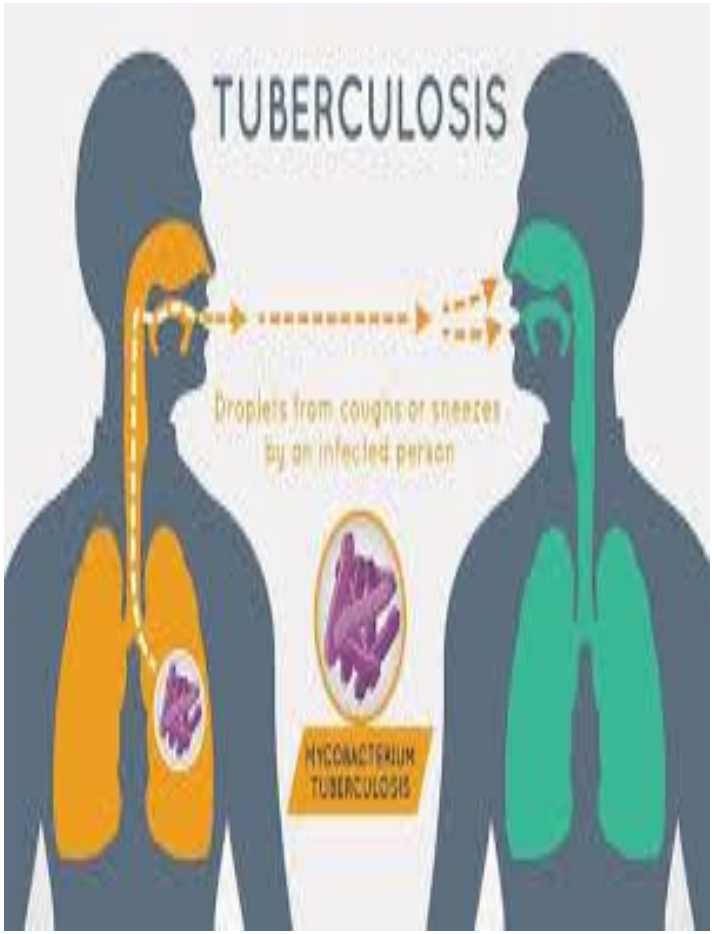
- Other previously treated:in this pts have been treated previously for TB and whose outcome aftertheir most recent course of treatment is unknown / ununundocumented.

- **Classification based on resistance:**
- 1. Mono-resistance
- 2. Poly-resistance
- 3. Multi-drug resistant TB (MDR-TB)
- 4. Extensively Drug Resistant TB (XDR-TB)
- 5. Rifampicin resistance (RR)

- **1. Mono-Resistance**: Resistance to one first line anti-TB drug only.
- **2. Poly Resistance:** Resistance to more than one first line anti-TB drugs, other than INH and Rifampicin together.
- **3. Multi-drug Resistant TB(MDR-TB):** Resistance to at least INH and Rifampicin, the two most potent anti-TB agents, with or without resistance to other first line drugs.

- **4. Extensive drug resistance(XDR-TB):** Refers to MDR-TB with additional resistance to Moxifloxacin or Levofloxacin and to one of two other group A drugs (BDQ, LZD)
- **5.RR TB:** Refers to resistance to Rifampicin detected using phenotype or genotype method.

Transmission of TB



- As this is an **airborne disease**
- Persons become infected with TB when they **inhale droplet nuclei** that contain **tubercle bacilli** and the bacilli begin to multiply in the lungs.
- It can also **spreads** to other parts of the body **via the blood stream, the lymphatic system or through direct extension to other organs.**

- **Tuberculosis of the lungs is the most frequent form of the disease, and**
- **Over 80%** of cases belong to this type.
- This is known as **Pulmonary tuberculosis.**
- **This form of TB can be infectious.**

- **TB affecting organs other than the lungs, most frequently:**
- **The pleura, lymph nodes, spine and other bones and joints, the genitourinary tract, the nervous system and abdomen is known as Extra Pulmonary TB.**
- TB may affect **any organ** and may even become **disseminated.** This type of TB is usually not infectious.

Risk factors

- **High risk for developing TB disease :**
- Medical condition(HIV,diabetes,silicosis,cancer, organ transplant ,CKD, immunosuppresive)
- Tobacco smoking
- Malnutrition
- Certain types of cancer (Leukaemia, Hodgkin's lymphoma)
- Infants & children ,<4 years
- Recent TB infection in last 2 years

Symptoms

Respiratory symptoms --

- Cough,
- Haemoptysis
- Chest pain,
- shortness of breath

General symptoms –

Night sweats, wt loss, fatigue, low grade fever.

- **S/S of extra pulmonary TB** :

TB lymphadenitis :swelling of lymph node

TB arthritis : joint pain ,swelling

TB meninges : headache ,fever, neck stiffness

Tools for Diagnosis of TB

- Sputum smear examination
- Radiological X-ray examination of the lungs : chest x-ray
- Tuberculin test (Mantoux test)
- Culture of TB bacilli
- Rapid molecular diagnostic test →Gene Xpert

Aims of treatment

- To render the patient non infectious ,break the chain of transmission and decrease pool of infection
- To cure the patient
- To prevent the relapse of TB
- To prevent the development of drug resistance

Anti Tubercular drug

First line drugs :	Second line drugs :	Newer drugs :
1. Isoniazid (H) 2. Rifampicin (R) 3. Pyrazinamide (Z) 4. Ethambutol (E)	I. Fluroquinolones II. Amikacin III. Capreomycin IV. Ethionamide V. Para aminosalicylic acid VI. Cycloserine VII. Thioacetazole	I. Linezolid II. Clarithromycin III. Azithromycin IV. Bedaquiline V. Delamanid

ANTITUBERCULAR DRUGS

ISONIAZID (INH)

- Isoniazid is the most active drug for the treatment of tuberculosis caused by susceptible strains.
- It is Tuberculospecific drug.
- It is a small molecule (MW137) that is freely soluble in water.
- It has structural similarity with pyridoxine.
- INH **Inhibit** hepatic cytochrome P450 enzyme

ANTITUBERCULAR DRUGS

- **Mechanism of action:**
- Isoniazid inhibits synthesis of mycolic acids, which are essential component of mycobacterial cell walls.
- Isoniazid is a prodrug that is activated by KatG, the mycobacterial catalase peroxidase.
- The activated form of INH form co-valent complex with an acyl carrier protein and a beta keroacyl carrier protein synthatase which blocks mycolic acid synthesis and kill the cell.

- **PHARMACOKINETICS:**
- **Absorption:** INH is readily absorbed from the GIT.
- **Distribution:** Readily distributed into all body fluids and tissues. The concentration in CNS and CSF ranges between 20% and 100% of simultaneous serum concentrations.
- **Metabolism:** Especially acetylation by liver N-acetyltransferase, is genetically determined.
- **Excretion:** INH metabolites and a small amount of unchanged drug are excreted mainly in the urine. The dose need not be adjusted in renal failure.

- **Adverse Drug Reactions:**
- The incidence and severity of unwanted reactions to INH are related to dosage and duration of treatment.
- **A.Immunologic Reactions:** Fever, skin rashes, drug induced SLE.
- B. Direct Toxicity: Hepatitis (most common major toxic effect).
- The risk of hepatitis is greater in individuals with alcohol dependence and possibly during pregnancy and the post-operative period.

- **ii.Peripheral Neuropathy:**
- Is observed in 10-20% of patients given dosage **greater than 5mg/kg/d**. but it is infrequently seen with the standard dose.
- Peripheral neuropathy is more likely to occur in **slow acetylators** and patients with predisposing conditions such as **malnutrition, alcoholism, diabetes, AIDS and uremia.**

ANTITUBERCULAR DRUGS

• RIFAMPICIN:

- Rifampicin is a semisynthetic derivative of Rifamycin, an antibiotic produced by **Streptomycis.**
- It is active in vitro against **gm(+ve) and gm(-ve) cocci, some enteric bacteria, mycobacteria and chlamydia.**
- Rifampicin strongly **induces** hepatic cytochrome P450 enzyme.

ANTITUBERCULAR DRUGS

- **Mechanism of Action:**
- Rifampicin binds to the **β-subunit of bacterial DNA dependent RNA polymerase and directly inhibit RNA synthesis.**
- Rifampicin is **bactericidal** for mycobacteria.
- It readily penetrates most tissues and penetrates into phagocytic cell.
- It can kill organisms that are poorly accessible to many other drugs, such as **intracellular organisms** and those **sequestered in abscesses and lung cavities.**

ANTITUBERCULAR DRUGS

- **PHARMACOKINETICS:**
- **Absorption:**Rifampicin is well absorbed after oral administration.
- **Distribution:** Distributed widely in body fluids and tissues.
- **Metabolism:** Liver
- **Excretion:** Excreted mainly through the liver into **bile** and a small amount excreted in the urine.
- **It then undergoes enterohepatic recirculation.**

- Dosage adjustment for renal or hepatic insufficiency is not necessary.
- Rifampicin is highly protein bound,
- and adequate CSF concentrations are achieved only in the presence of meningeal inflammation.

- **Adverse Effects:**
- 1.Rifampicin imparts a harmless orange colour to urine, sweat and tears.
- 2.Occasional adverse effects include rashes, thrombocytopenia and nephritis.
- 3.May cause Cholestatic jaundice and occasionally hepatitis.
- 4.It commonly cause light chain protenuria.

- 5.May cause Flu like syndrome characterized by fever , chills, myalgia, anaemia and thrombocytopenia.
- 6.Its use has been associated with acute tubular necrosis.

ANTITUBERCULAR DRUGS

• PYRAZINAMIDE

- Pyrazinamide is a relative of nicotinamide.
- It is stable and slightly soluble in water.
- It is **inactive at neutral pH, but at PH 5.5, it inhibits tubercle bacilli** at conc. of approximately 20mcg/ml.
- The drug is taken up by macrophages and **exert its activity against mycobacteria residing within the acidic environment of lysosome.**

- **Mechanism of action:**
- Pyrazinamide is converted to **pyrazinoic acid–** the active form of the drug—by mycobacterial **pyrazinamidase**.
- Pyrazinoic acid disrupts mycobacterial cell membrane metabolism and transport function.

- Pyrazinamide is an important front-line drug used in conjunction with INH and Rifampicin in short course (6month) regimen:
- As a **sterilizing agent** active against **residual intracellular organisms** that may cause **relapse.**

- **PHARMACOKINETICS:**
- **Absorption:** Well absorbed from the GIT.
- **Distribution:** Widely distributed in body tissues, including inflamed meninges.
- **Half life:** 8-11hours.
- **Metabolism:** Liver
- **Excretion:**Kidney

- **Adverse Reactions:**
- Hepatotoxicity (1-5%) of patients.
- Nausea, vomiting ,drug fever.
- **Hyperuricemia (may provoke acute gouty arthritis.)**

- **ETHAMBUTOL:**

- Ethambutol is a synthetic, water soluble, stable compound.
- **Mechanism of action:**
- Ethambutol inhibits mycobacterial **Arabinosyl transferase enzyme.**
- Arabinosyl transferase are involved in the polymerization reaction of **arabinoglycan** , an essential component of the mycobacterial cell wall.

- **PHARMACOKINETICS:**
- It is well absorbed from the gut
- About 20% of the drug is excreted in feces and 50% in urine in unchanged form.
- Ethambutol accumulate in renal failure and the dose should be reduced by half , if creatinine clearance is less than 10ml/min.
- Ethambutol crosses the BBB only when the meninges are inflamed

- **Adverse Effects:**
- Hypersensitivity to Ethambutol is rare.
- **The most common serious adverse effect is retrobulbar neuritis,** resulting in loss of visual acuity and red-green color blindness.
- **Periodic visual acuity testing** is desirable if the 25mg/kg/d dosage is used.
- Relatively **contraindicated in children too young** to permit assessment of visual acuity and red-green color discrimination

- Resistance to Ethambutol emerges rapidly when the drug is used alone.
- Therefore it is always given in combination with other antitubercular drugs.

Treatment of TB

Standardized treatment regimen for each diagnostic category (adults)

TB diagnostic category	Type of Patient	Treatment regimen	
		Intensive phase (Daily)	Continuation Phase (Daily)
New Cases (never been treated for TB or have taken ATT for < 1 month)	Bacteriologically positive PTB patients	2 (HRZE)	4 (HR)
	Bacteriologically negative PTB patients		
	Extra-pulmonary TB*		
	TB/HIV co-infected		
Previously Treated Cases (received ≥ 1 month of ATT in the past) **	If no resistance to TB drugs (both H and R sensitive P and EP TB Cases)	6 HRZE	
	Clinically diagnosed PTB	6 HRZE	
	Complicated EP cases (TB meningitis, Neurological TB, Bone TB, non-resolving lymph node)	12 HRZE-Lfx	
	If Rif susceptible and INH resistant or unknown in bacteriologically confirmed PTB & EP-TB	6 (H)REZ- Lfx	

Treatment category for all TB patient

- **New TB patient**

All drug sensitive TB patient whether bacteriologically confirmed / clinically diagnosed will receive the standard treatment regimen ,comprising of 4 drugs – HRZE – for 2 months (initial phase)

The treatment maybe extended in certain form of extrapulmonary TB , spinal tb,CNS tb , disseminated TB etc.

For Previously treated Tb

If the pt is susceptible to both Rifampicin & Isoniazid ,all bacteriologically confirmed previously treated pulmonary as well as Extrapulmonary Tb patients will be given Cat – I

- all clinically diagnosed pulmonary TB cases with a history of previous treatment will be given 6 HRZE for 6 months,.

Treatment phase

- **Intensive phase**

Administered daily for the initial 2 months of treatment .

The objective of combining 4 drug is— to achieve rapid killing of multiply bacillary population.

- **Continuation phase**

Administered for 4 months with 2 FDC and is essential to eliminate remaining bacterial population which are largely responsible for the relapse.

- If Rifampicin resistance is detected an MDR TB regimen should be prescribed according to recent drug resistane TB treatment guidelines.

- **Regimen for Rifampicin susceptile & isoniazid resitant--- 6-H-R-Z-E-Lfx**

ANTITUBERCULAR DRUGS

- **Fixed dose combinations the management of (FDCs) TB patients .**
- In the management of TB patients with first line drugs, **fixed dose combinations (FDCs) of anti-TB drugs** are recommended over individual drugs.
- **Fixed dose combinations refer to products containing two or more active ingredients in fixed doses, used for a particular indication(s).**
- Tablets of fixed dose drug combinations have several advantages compared to individual drugs.

Fixed dose combination

- **Advantages** :
- Prescription errors are likely to be less errors .
- Drug resist. Less likely to occur .
- It helps simplify drug management .

- **Disadvantages :**
- Risk of over dosages & under dosages occuring
- Poor Rifampicin bioavailability is a problem with low quality.

- **FDC tablets are composed as –**
- 4 FDC : Isoniazid 75 mg +Rifampicin 150 mg + Pyrazinamide 400 mg + Ethambutol 275 mg

- 2 FDC :Isoniazid 75 mg + Rifampicin 150 mg

Drug dosages & frequency

- Treatment dosages are based on wt. bands .
- Drugs should be given daily . Intensive phase is for 2 months (60 doses) .
- Intensve phase is stopped after the pt complete 60 doses .this phase shouldn’t be extended beyond 60 doses for any reasons.
- Continuation phase is daily for 4 months (120 doses)

Monitoring of treatment

- **Bacteriological monitoring of PTB** : sputum examination are carried out at the end of 2nd month .(end of IP). At the end of 5th month at the end of Rx 6th month.
- If an EP case on Rx develop chest symptoms then his /her sputum should be collected and sent for Gene Xpart
- clinical monitoring : by checking for symptomatic wt gain ,especially in the case of EP .

Schedule for follow up

- Intensive phase – sputum smear examination at End of 2 month →

➢ If smear negative –start pt on CP

➢ If smear positive -- test on Xpert MTB →

1) If Rifampicin sensitive –start pt on CP
2) If Rifampicin resistance –declare RX failure & start drug resistance TB management.

- **Continuation phase :**

#sputum smear examination

at end of month five :

If smear neagative →cont. CP

#sputum smear examination negative

at end of month 6→ declare cure.

sputum smear examination positive →declare Rx failure & evaluate for drug resistance

Treatment for extra pulmonary TB

- All EP TB pt will receive the same Rx as PTB & the total duration also same.
- **TB lymph node** : if there's no improvement in TB lymphadenitis even after 6 month of Rx, then on the basis of clinical judgement , the CP maybe extend upto 10 months.
- **TB Meningitis** : the duration of Rx is 12 month bcz of the uncertain penetration of blood brain barrier by some anti TB drug .

- It is also recommended that all pt with TB meningitis ,an initial adjuvant corticosteroid therapy with dexamethason or prednisolon tapered over 6-8 wks. Most frequently drug used is Prednisolon , in the case of severely ill pt for 4 weeks.

- **Osteoarticular TB & Spinal TB(Pott's disease)**

12 months with 2HRZE or, 10 month HR

TB in special situation

- **Pregnancy** : anti TB Rx should be started as soon as the dx made . Most anti TB drug are safe to use during preg.
- All pregnant woman should also receive preventive treatment for Isoniazide related peripheral neuropathy . For this they should be given Vit B6 for the entire duration of Rx
- Rifampicin can increase metaboilism of vit K . Resulting in clotting disorder . Prophylactic adminstration of Vit k to the mother & neonate is recommended to prevent the risk of post natal Hg.

- **Breast Feeding Women:**
- Breast Feeding mothers with TB should receive the full course of Anti-TB treatment. Proper treatment is the best way of preventing transmission of TB to the baby.
- All Anti-TB drugs are compatible with breast feeding.

- **Management of a new-born child of a mother with active TB:**
- If the mother is **sputum smear negative**, and if the infant **has no evidence of congenital TB, BCG is given to the infant.**
- If the mother is **sputum- smear positive at the time of delivery, infant should be carefully examined for evidence of active disease.**
- **If the infant is ill at birth and congenital TB is suspected, a full course of Anti-TB treatment should be given.**

- **If the infant is ill at birth and congenital TB is suspected,**

a full course of Anti-TB treatment should be given.

- **If the child is well,**

give prophylactic treatment of daily INH and Rifampicin for 3 months(3RH regimen) at recommended dosages. BCG is withheld till completion of prophylactic treatment.

- The **Mantoux skin test** is done after 3 months of prophylactic treatment.

Adverse effect & management

- **Isoniazid** : Burning / tingling sensation or numbness in limbs
- Mx : give pyridoxime 100 mg daily

- **Pyrazinamid** : Arthralgia / joint pain ,elevated serum Uric acid level .
- Mx : anti inflammatory agent (paracetamol,ibuprofen etc) , anti Hyperurecaemic agent .

- **Most anti TB drug causes Hepatitis (especially Isoniazid , Rifampicin, Pyrazinamid):**

- Mx : monitoring of liver function ;
- If pt assymptomatic , but liver enzyme are elevated to less than five times the normal values ,cont Anti TB therapy . But conduct weekly LFT.
- If liver enzyme are elevated to more than five times the normal limits ,stop all anti TB medication .if liver enzyme cont. increase then unrelated cause must be excluded.

- **Ethambutol** : visual impairement :
- Mx : usually reversible after discontinuation of the drug.

THANK

YOU

ALL ☺