01.ABSTRACT: -

Tuberculosis (TB) is a major global infectious disease caused mainly by Mycobacterium tuberculosis. It continues to be a leading cause of death, especially in developing countries, and the problem is worsened by HIV co-infection, long treatment duration, drug toxicity, and the rise of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Current treatment uses first-line drugs such as isoniazid, rifampicin, pyrazinamide, and ethambutol, given in two phases over six months. However, treatment failure often occurs due to poor patient compliance, side effects, and the inability of existing drugs to kill dormant bacteria.

New and emerging anti-TB drugs including fluoroquinolones, rifamycin derivatives, oxazolidinones, nitroimidazoles, diarylquinolines, and others aim to shorten therapy, overcome resistance, and target persistent bacterial populations. Modern approaches such as nanoparticle-based drug delivery systems offer promising solutions by improving drug absorption, reducing dosing frequency, lowering side effects, and increasing patient compliance. Both synthetic (e.g., PLGA) and natural (e.g., liposomes, alginate, chitosan) nanoparticles have shown strong results in animal studies.

Treatment guidelines have evolved over time, focusing on rational drug combinations, drug susceptibility testing, and careful use of second-line drugs to prevent resistance. Special situations such as pregnancy, diabetes, renal failure, HIV co-infection, and severe disease require modified therapy. Additionally, the role of immunomodulators—including cytokines like IL-12, IFN-γ, TNF-α, and non-cytokine immune boosters such as vitamin D—continues to be explored to enhance the host immune response.

KEYWORDS: - Tuberculosis (TB), Mycobacterium tuberculosis, First-line drugs, Drug resistance (MDR-TB, XDR-TB), Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, Nanoparticles, Drug delivery systems, PLGA nanoparticles, Liposomes, New anti-TB drugs, Fluoroquinolones, Oxazolidinones, Diarylquinolines (TMC-207), Nitroimidazoles (PA-824), TB

chemotherapy, HIV co-infection, Treatment guidelines, Cytokines, Immunomodulators, Vitamin D, Drug toxicity, Compliance.

02.INTRODUCTION: - [1]

Tuberculosis (TB) is one of the top diseases that causes death even though it can be treated. It kills around 5,000 people every day, and the WHO reported 1.8 million deaths in 2008. TB is caused by bacteria from the Mycobacterium group. There are more than 60 species in this family, but only a few like Mycobacterium tuberculosis M. leprae, M. africanus, and M. avium are harmful to humans.

Mycobacterium tuberculosis can stay inside the human body for many years without causing symptoms. This is called the latent stage. When a person's immune system becomes weak due to old age, another illness, or HIV infection the bacteria can become active again.HIV makes the immune system weak, so TB and HIV together make the condition worse and can increase the chance of death.

How TB Spreads

TB spreads easily when it is in the active stage. A person can get infected just by inhaling 10 bacteria. When the bacteria enter the lungs, they are usually taken up by alveolar macrophages. But MTB can escape the immune system and stay inside the body in both slow-growing and fast-growing forms.
This makes treatment difficult because most antibiotics kill bacteria only when they are actively dividing.

TB Treatment

TB is treated with first-line drugs (FLDs): -

- Isoniazid (INH)
- Rifampin (RIF)

- Pyrazinamide (Ethambutol (ETH)

The treatment has two phases: -

1. **Intensive phase (2 months): -**

   All four drugs are used to kill the fast-growing bacteria. This helps reduce symptoms quickly.

2. **Continuation phase (4 months): -**

   Only INH and RIF are given to kill the slow-growing bacteria that are still left.

Why TB Treatment Sometimes Fails

Even though these medicines work well, treatment often fails because:

- The treatment lasts a long time (6 months)
- Many drugs have to be taken
- Patients may stop taking medicines early, leading to treatment failure and drug resistance.

PRINCIPLES OF TB CHEMOTHERAPY: - [1]

The main aim of tb treatment is to help the patient get better and also to protect the community. when treatment is started on time, it quickly kills the bacteria that are multiplying in the body. this reduces symptoms and the chances of death. within a few days of treatment, the number of live bacteria drops a lot, which makes the patient much less infectious to others. modern tb treatment plans are made to stop the spread of infection, kill all remaining bacteria, and prevent drug resistance.

Tb can affect any organ, but lung tb is the most common. in lung cavities, tb bacteria exist in three groups. the first group contains many bacteria growing actively in the liquid of the lung cavity. this

is where drug-resistant bacteria can develop because there are so many organisms. the second group grows slowly inside macrophages; these bacteria are fewer and harder to kill because the acidic environment reduces the effect of many drugs. the third group also grows slowly in solid caseous material, where drugs may not reach easily due to poor blood supply. to treat tb properly, the drug combination must kill bacteria in all these areas, and treatment must continue long enough to remove all living germs. in the early days, streptomycin was used alone, but even though patients improved at first, many got sick again because the bacteria developed resistance. resistance to each Tb drug naturally appears at a rate of about 1 in 1 million to 1 in 10 million bacteria. since there are so many bacteria in lung cavities, using only one drug can lead to resistance. therefore, multiple drugs are always used together to prevent this.

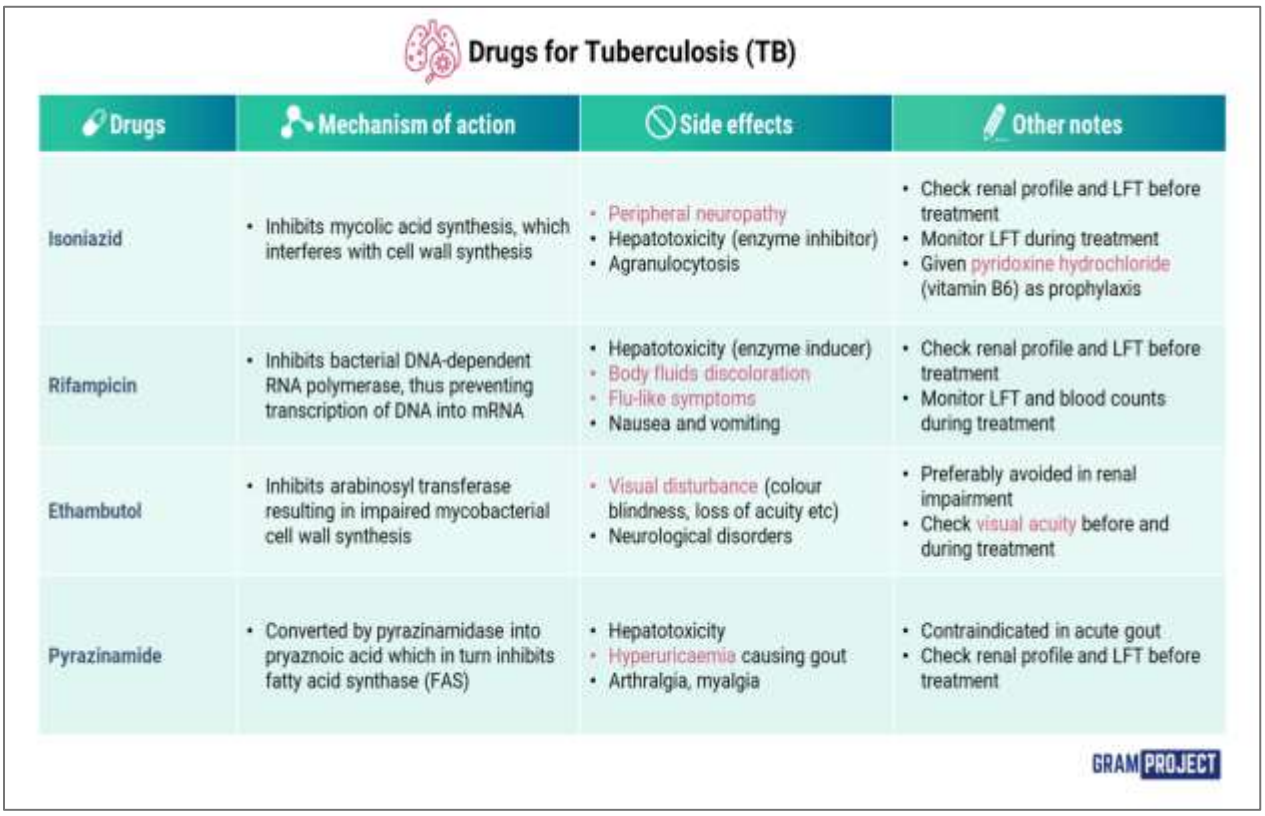

Table No. 01: - Tuberculosis Drug

Reference: - [6]

Tb treatment has two phases: an 8-week intensive phase and a continuation phase of 4–7 months. the intensive phase uses rifampin, isoniazid and pyrazinamide to clear most bacteria to prevent relapse. treatment should be started as soon as signs and x-ray findings suggest active tb.

doctors should not delay treatment while waiting for lab confirmation, especially in very sick or immunocompromised patients.

EXISTING AND EMERGING DRUGS: FIRST-LINE DRUGS: - [1]

The commonly used medicines isoniazid (INH), revamping (RIF), pyrazinamide (PZA), and ethambutol (ETH) are known as first-line drugs (FLDs). These drugs work well against TB bacteria that are drug sensitive, and even today INH and RIF are the most powerful medicines against Mycobacterium tuberculosis. Among all the FLDs, only pyrazinamide can act on the persistent (slow-growing) bacteria, but none of these drugs can kill the dormant bacteria that cause latent TB.

If these dormant bacteria are not removed, they can reactivate later when the immune system becomes weak. In many other bacterial infections, the few bacteria left after antibiotic treatment are killed by the body's immune system. However, in TB this does not happen because the patient's immune system is already weak, and the TB bacteria continue to interfere with the immune response. Because of this, even when the bacteria are drug-sensitive, TB treatment takes around 6 months. A brief summary of how each first-line drug works and its activity is usually provided separately.

03.NEW AND EMERGING DRUGS: - [1]

1.Fluoroquinolones: Fluoroquinolones include drugs like ofloxacin, ciprofloxacin, Gemifloxacin, moxifloxacin, and others. Although some of these drugs were discovered long ago, their anti-TB activity has only been recognised recently. These medicines have good pharmacokinetic properties, meaning they stay in the body for a long time and may allow less frequent dosing.

They also enter body tissues very well, including macrophages, which are the main cells where TB bacteria stay. When used alone, they generally show fewer side effects. However, moxifloxacin can cause serious toxicity when given together with rifampicin (RIF) and pyrazinamide (PYZ), because RIF and PYZ together can cause harmful liver effects. Even though this combination caused toxicity, it performed better than the INH–RIF–PYZ combination in mouse studies. Moxifloxacin is currently in phase 3 clinical trials conducted by the TB Alliance. Many fluoroquinolones are already used as second-line drugs for TB, but resistance to these drugs is rising rapidly. For example, in the Philippines, 51% of MDR-TB cases showed resistance to both ciprofloxacin and ofloxacin.

2.Rifamycin Derivatives: -A practical strategy for discovering new anti-TB drugs is to modify existing first-line drugs to improve their activity, reduce toxicity, and avoid resistance.

Rifamycin derivatives such as rifabutin, realize, and rifapentine are modified forms of rifampicin (RIF). These drugs are usually more active than RIF. Rifabutin is 4–8 times more effective against

M. tuberculosis, has a longer half-life, and enters tissues better. It also causes fewer drug interactions, making it suitable for TB patients who are also taking HIV medicines. For this reason, the CDC (USA) recommends rifabutin instead of RIF in TB patients with HIV. Rifalazil is even more powerful; in laboratory studies, it is 100 times more active than RIF and has shown stronger effects in mouse models. In humans, taking rifalazil once a week with daily INH was found to be more effective than daily RIF and INH, without causing major side effects.

3.Oxazolidinones: -Oxazolidinones are a group of drugs with broad antimicrobial activity, and some are already available for medical use. They have shown good results against TB in mouse models. These drugs work by blocking early protein synthesis in TB bacteria, and drug resistance develops slowly. The second generation of oxazolidinones has lower toxicity than the first generation while maintaining strong antimicrobial activity. Linezolid and PNU-100480 have both shown good effects in animal studies. Linezolid has also been used "off-label" to treat MDR-TB and XDR-TB in humans when other drugs fail.

4.Nitroimidazoles: -Nitroimidazoles are a new group of anti-tb drugs, and the most important one is pa-824. this drug can stop both protein and fat (lipid) production in the tb bacteria, so it can kill both active and sleeping (dormant) bacteria. because of this, it may work for both active and latent tb. pa-824 is now in phase ii clinical trials, but like other nitroimidazoles, it can still cause mutation or cancer, though less than older drugs, which is a safety concern.

5.Azole: - Azole drugs like miconazole and clotrimazole also show activity against tb by targeting a special enzyme (cytochrome p450) in the bacteria. the study of this enzyme has helped researchers to develop new drugs.

6.Diarylquinolines: - Diarylquinolines, with tmc-207 as the main drug, are very effective against all types of tb bacteria, including drug-sensitive and drug-resistant strains. tmc-207 is the first drug tested for both types and has shown good results in mdr-tb with acceptable side effects. it works by blocking atp synthase, an enzyme needed for energy production in tb bacteria.

7.Phenothiazines: - Phenothiazines like chlorpromazine and thioridazine are mainly antipsychotic medicines but also have anti-tb effects. they can kill both drug-sensitive and drug-resistant tb bacteria, partly because they collect inside macrophages where tb bacteria usually stay.

8.Peptide deformalize inhibitors: -Peptide deformalize inhibitors are another new group. this enzyme is important for bacteria to process new proteins, but it is not important in humans. this makes it a good possible target for future tb drugs. however, even though it is essential in the bcg strain, it does not work very well on the slow-growing tb bacteria.

04.ROLE OF NANOPARTICLES IN ANTI-TB DRUG DELIVERY: - [1]

Studies show that many tb patients do not take their medicines regularly. the main reason is that tb treatment needs many pills every day and must be continued for many months. because of this, patients often stop the treatment in between. this can make the disease worse and increase side effects. to help patients follow the treatment properly, we need to either reduce the treatment time or reduce how many pills they take daily. this is possible by using new formulation methods.

Nanoparticles can be made from man-made (synthetic) or natural materials. synthetic materials include plug, polylactic acid, and polyglycolic acid. natural materials include liposomes, alginic acid, chitosan, and gelatine. the choice of material depends on how the drug will be given, how fast it needs to be released, and the properties of the drug. all these materials are biodegradable, which means they break down easily inside the body and are safely removed.

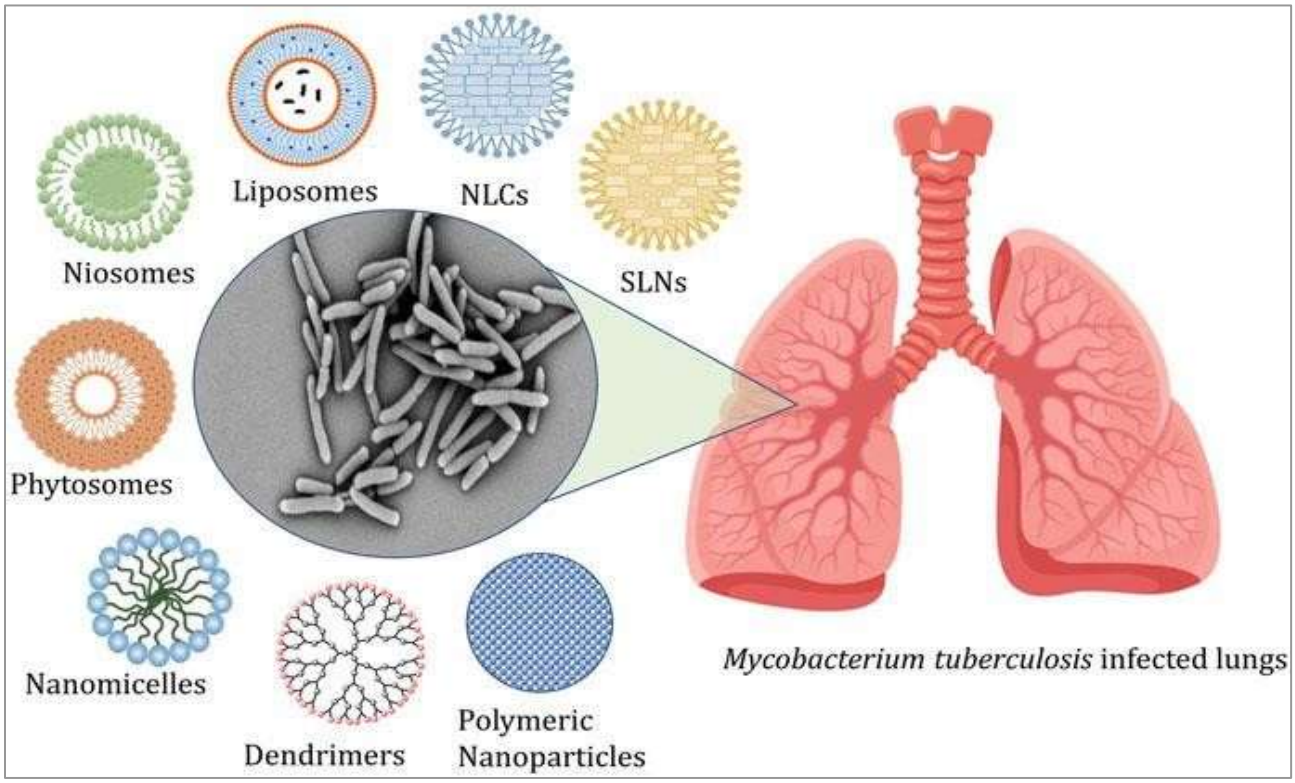

Fig.no.01: - Mycobacterium tuberculosis

Reference:- [7]

05.CURRENT ANTI-TUBERCULOSIS CHEMOTHERAPY: - [2]

Current TB treatment mainly depends on anti-TB medicines because prevention methods like the BCG vaccine and chemoprophylaxis are not fully effective. The aim of treatment is to cure the patient completely, prevent death, stop the spread of TB, and avoid drug resistance. TB must always be treated with a combination of drugs for a long period because using a single drug or adding one drug to a failing treatment can lead to multidrug-resistant TB (MDR-TB). According to WHO, treatment starts with a 2-month intensive phase using rifampicin, isoniazid, pyrazinamide, and ethambutol every day, followed by a continuation phase of rifampicin and isoniazid for another 4 months. INH, along with streptomycin and ethambutol, kills most fast-growing bacteria in the first two weeks, while rifampicin and pyrazinamide help kill the slow-growing and semi-dormant bacteria that remain in the body. INH and RIF together kill more than 99% of TB bacteria within two months, which allows the total treatment duration to be reduced from 18 months to 6 months.

However, resistance to these drugs is a big problem because it makes treatment less effective, more toxic, and more dangerous, especially in HIV-positive patients. TB treatment also faces challenges such as many tablets to take, side effects, poor patient adherence, and slow recovery.

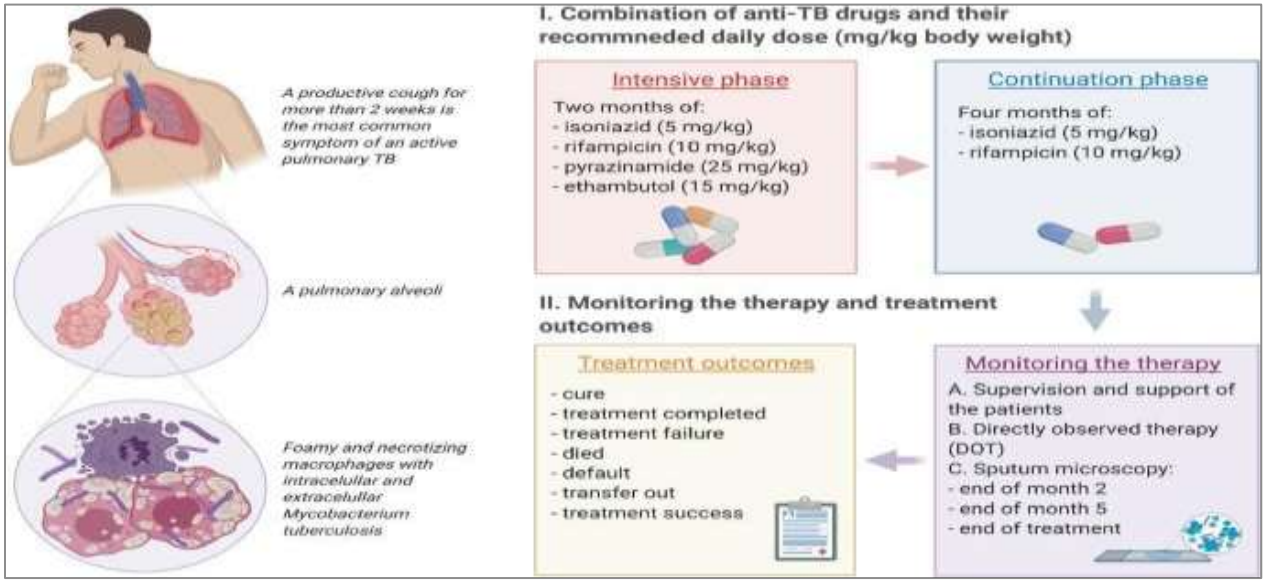

Fig.no.02: -

Reference: - [8]

SYNTHETIC NANOPARTICLE MATERIALS: - [3]

Many scientists are trying to improve anti-tb treatment by using modern drug delivery systems. in one study by Pandey et al., three main anti-tb drugs inh, riff, and pyz were packed inside plug nanoparticles (plug-np) and given orally to tb-infected mice (once every 10 days). these results were compared with the normal daily free drug doses. In the plug-np group, the minimum inhibitory concentration (mic) level stayed in the blood for 6– 9 days and in organs (liver, lungs, and spleen) for 9 days. but in the normal free drug group, the same level lasted only 12–24 hours. also, no bacterial load was found in the plug-np treated mice, compared to the untreated group. the same researchers got similar results in guinea pigs and in mice using inhalable plug-np. none of the studies showed any hepatotoxicity.

NATURAL NANOPARTICLE MATERIALS: - [3]

In another study, inh and rif were packed inside liposomes tagged with o-stearyl amylopectin and given intravenously to infected mice. this tagging helps the drug target the lung tissue.

The bacterial load was cleared within 6 weeks using weekly dosing and only one-third of the regular therapeutic dose, with no hepatotoxicity.

Similar long-lasting drug action, with less frequent dosing and smaller drug quantity, was seen when drugs were encapsulated in alginic acid–chitosan nanoparticles.

Pandey et al explained the main advantages of these natural materials over synthetic ones. some benefits include:

- no need for expensive organic solvents
- high water content
- high gel porosity
- some materials are already approved for use in other formulations

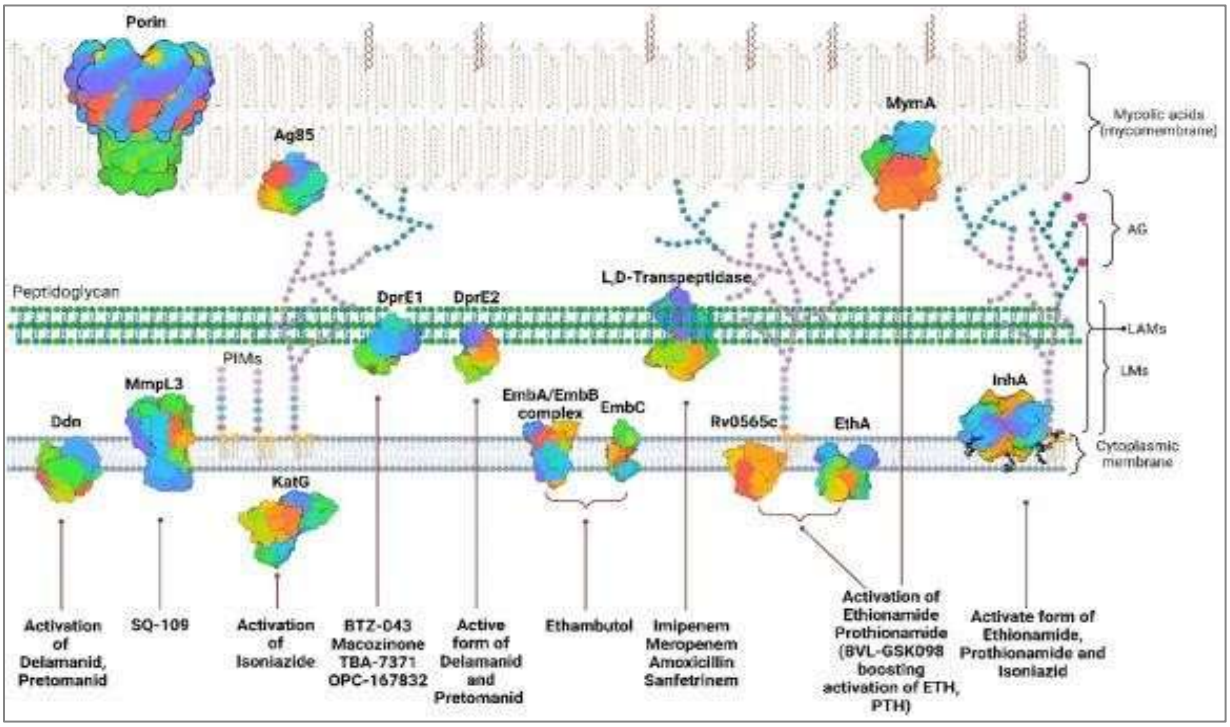

Fig.no.03

Reference: - [9]

This image shows how different anti-tb (tuberculosis) drugs work inside the tb bacteria. the picture displays the many layers of the bacterial cell wall and the important enzymes that help the bacteria build and protect itself. each coloured protein in the image is an enzyme, and the arrows show which drug works on which enzyme. some drugs, like isoniazid, ethionamide, dexaminid, and pteromalid, first need to be activated by special bacterial enzymes before they can work. other drugs, such as ethambutol, btZ-043, sq-109, and carbapenem antibiotics, directly block enzymes that help form the bacteria's cell wall. by blocking these enzymes, the drugs stop the bacteria from growing, repairing itself, or surviving. overall, the diagram explains that each anti-tb drug has a specific target inside the tb bacteria, and by attacking these targets, the drugs help kill the bacteria effectively.

06.TREATMENT GUIDELINES: PAST, PRESENT AND FUTURE: - [5]

The treatment of tuberculosis (tb) has changed over the years based on research and recommendations from the world health organization (who). before 2009, who divided tb treatment into four categories to guide doctors. category 1 was meant for new tb patients and included four main first-line drugs ethambutol, isoniazid, rifampicin, and pyrazinamide for the first two months, followed by isoniazid and rifampicin for the next four months. this regimen was very effective because it killed a large number of bacteria quickly, helped patients become non-infectious within two months, and showed very low relapse rates. category 2 was used for retreatment cases, such as patients who had relapsed. this regimen added streptomycin during the first two months, but later it was criticized because it was based more on expert opinion than solid scientific evidence. in many countries, where drug resistance was already high, this regimen did not work well and sometimes made the problem worse by adding only one new drug to a failing treatment plan, which is against the principles of tb therapy.

Category 3 was recommended for children and for smear-negative or extra-pulmonary tb cases who were thought to have fewer bacteria. ethambutol was removed in this group because doctors assumed the risk of resistance was low. however, since isoniazid resistance is common in many areas, who changed its recommendation in 2004 and suggested adding ethambutol back even for these patients. category 4 focused on treating drug-resistant tb (dr-tb) using stronger second-line drugs. these drugs had to be given for a much longer time, often 18–24 months, and had more side effects. for extremely drug-resistant tb (xdr-tb), even stronger combinations with drugs like capreomycin, moxifloxacin, and para-amino salicylic acid were needed. Because these four treatment categories created confusion and had several limitations, the who revised the guidelines in 2009 to simplify treatment and improve patient outcomes. however, the updated guidelines also suggested giving second-line drugs earlier in some retreatment cases.

While this helped in areas with high multidrug-resistant tb (mdr-tb), it also increased the risk of misusing second-line drugs and causing even more dangerous resistance like xdr-tb or totally drug-resistant tb (TDR). therefore, many experts believe that treatment should be carefully planned.

New patients should always be given the standard regimen, while relapse cases should start first-line therapy again and undergo drug susceptibility testing (DST).

If DST is not available but the patient responds well in the first few weeks, the same treatment may be continued instead of rushing into second-line drugs. this careful approach helps prevent unnecessary resistance and protects the effectiveness of important tb medicines.

07.CHEMOTHERAPY OF TB IN SPECIAL SITUATIONS: - [5]

1.Pregnancy: -

Rifampin, isoniazid, ethambutol, and pyrazinamide are safe to use during pregnancy. streptomycin should not be used because it can damage the baby's ears (ototoxicity).
pregnant women should take pyridoxine (vitamin b6) 10 mg/day to prevent nerve problems caused by isoniazid.

2.Diabetes mellitus: -

Normal tb treatment is used. blood sugar should be well controlled. doses of oral anti-diabetic drugs may need to be increased because rifampin reduces their effect. pyridoxine 10 mg/day is advised to prevent isoniazid-related nerve problems.

3.Renal failure: -

Dose adjustment is needed for streptomycin, ethambutol, and isoniazid based on creatinine clearance. in acute renal failure, ethambutol should be given 8 hours before haemodialysis.
creatinine clearance is estimated using the formula:
creatinine clearance = (140 – age) × weight / (72 × serum creatinine) based on
the value, the dose interval can be changed or the dose can be reduced.

4.Post-transplant patients and other special cases: -

Rifampin is avoided because it increases the clearance of cyclosporine, reducing its effect.

5.Pre-existing liver disease: -

If liver enzymes are normal and disease is stable, all anti-tb drugs can be used, but liver function must be monitored frequently.

6.Patients who are unconscious or unable to swallow: -

If the patient is fed by nasogastric or gastrostomy tube, usual drugs can be powdered and given, but feeds should be avoided 2–3 hours before and after giving the medicines.
if the patient is on parenteral nutrition or after enterostomy, intramuscular streptomycin and intravenous quinolones may be used until oral feeding starts again.

7.Tb with HIV co-infection: -

In early HIV stages, tb looks similar to tb in HIV-negative people. in
later stages, extra-pulmonary and widespread tb is common.
diagnosis is difficult because other infections are common and the tuberculin test may be negative. standard short-course tb treatment is used, response is good, but relapse is more common.

8.Seriously ill patients with suspected tb: -

Specific empiric anti-tuberculosis therapy (seat) may be used.

isoniazid, ethambutol, and pyrazinamide are started based on clinical and radiological suspicion when no lab proof is available.

08.FOLLOW-UP AND EXPECTED RESPONSE TO ANTI-TB THERAPY: -

[5]

Anti-tb treatment mainly works by killing the tb germs and cleaning the infected area. to check if treatment is working, doctors prefer smear and culture tests.
in extra-pulmonary tb, if these tests cannot be done, doctors simply follow the standard treatment regimen.

Tb shows a range **(spectrum)** of disease depending on how strong the person's immunity is:

- **RR (reactive)** – nodules in x-ray
- **RI (reactive intermediate)** – nodules + cavities
- **UI (unreactive intermediate)** – widespread fibro cavitary disease
- **UU (unreactive)** – disease spread all over the body

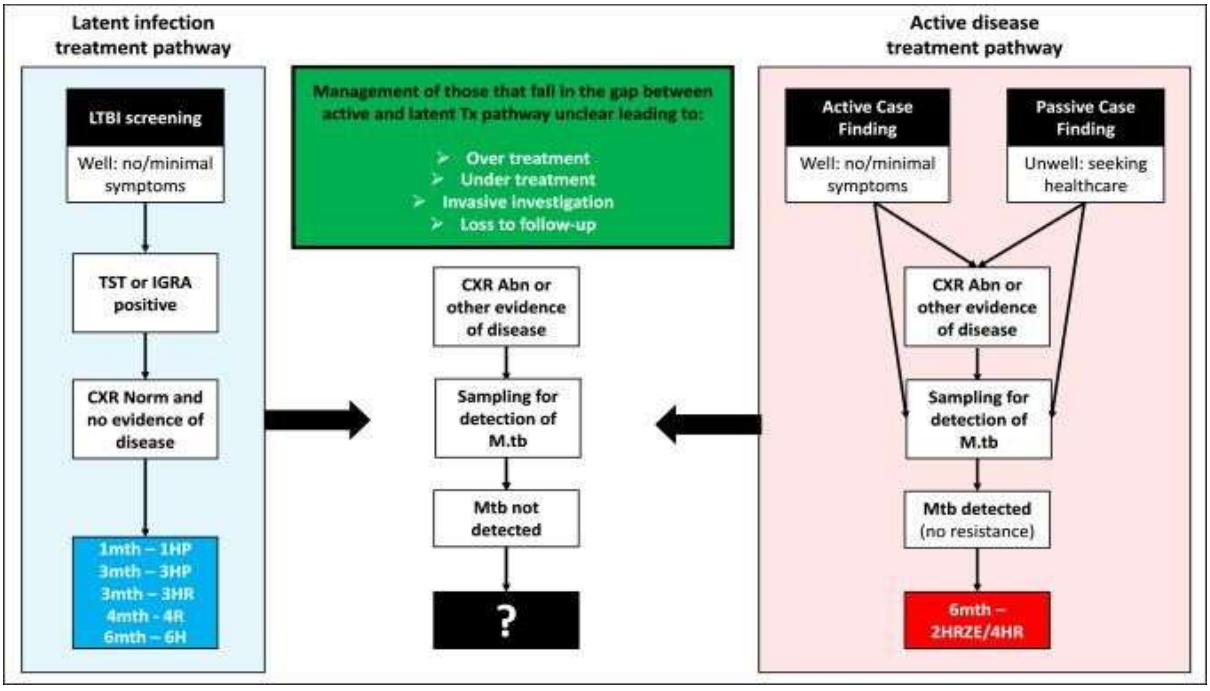

Fig.no.05

Reference: - [10]

Examples of paradoxical response:

- **Tb lymph nodes**: new nodes may appear, old nodes may get bigger, cold abscess or sinus can form. even after treatment, around **10%** people still have leftover nodes.
- **Tb meningitis**: complications like hydrocephalus, tuberculomas or abscess may happen and cause worsening even though treatment is correct.
- **Other problems** during or after treatment: bronchopleural fistula, empyema, or haemoptysis.

- **Important:** anti-tb medicines cannot stop or cure these immune-related or mechanical complications. Some patients may need steroids **or** surgery**,** but the at treatment should not be changed or extended**.**

09.MANAGING DRUG TOXICITY TO ANTI-TB THERAPY: - [5]

Gastrointestinal intolerance

Nausea from tb medicines usually improves on its own. if it continues, the patient can take the medicines 2 hours after breakfast or at bedtime (2–3 hours after dinner). this helps the patient sleep through the side effects. in serious cases, doctors may give h2 blockers or proton pump inhibitors. these medicines do not affect tb drug absorption, unlike prokinetic drugs.

Itching and skin rash

Itching or rash from tb drugs is usually mild if there is no fever or liver problem. in such cases, doctors give antihistamines and calamine lotion. tb treatment can be continued.

Drug hypersensitivity

Almost all tb drugs can cause allergy. it may show as fever, joint pain, skin reactions, hepatitis, swollen lymph nodes or spleen. if a patient develops new fever after starting tb treatment, it may be allergy. all tb drugs should be stopped at once. if fever drops within 24 hours, hypersensitivity is confirmed. later, drugs are restarted one by one to find the drug causing the reaction. that drug is then removed and a new treatment plan is used.

Hepatotoxicity (liver damage)

liver damage from tb drugs occurs in three types:

1. mild increase in liver enzymes — common and goes back to normal even if treatment continues.
2. dose-related liver problems — happen if the patient gets higher doses than needed.
3. rare serious hepatitis due to isoniazid or rifampicin — may lead to liver failure.

Drug-induced hepatitis looks like viral hepatitis. it usually appears within 2 months but can come later too. if viral tests are not available, doctors assume it is due to the tb drugs. if liver enzymes rise more than 4 times normal or bilirubin increases, all liver-toxic drugs must be stopped immediately.

Thrombocytopenia (low platelets)

rifampicin is the most common cause, but ethambutol can also cause low platelets. patients may show small red spots (petechiae) or bleeding. platelet count will drop within 24 hours of taking the medicine. earlier, reuse of rifampicin was avoided after this reaction, but new studies show it can sometimes be restarted under careful medical supervision.

10.CYTOKINES AND NON -CYTOKINES MODULATORS: - [6]

Cytokines are powerful chemicals made by immune cells, and they act as important immunomodulators during mycobacterial infections. in tb, the th1 type of immune response, which is part of cell-mediated immunity, is most important for protection. therefore, cytokines that promote th1 response help in giving better immunity. il-12 is one such cytokine. during tb infection, il-12 increases the production of interferon-gamma (ifn-γ), tumour necrosis factor-alpha (tnf-α) and granulocyte-macrophage colony-stimulating factor, all of which activate natural killer (nk) cells and strongly push the immune system towards a th1 response. studies in mice showed that giving extra il-12 increases resistance to mtb infection, while mice lacking il-12 become more susceptible. defects in the il-12 receptor gene make humans highly sensitive even to weak mycobacteria like the bcg vaccine strain, a condition called mendelian susceptibility to mycobacterial disease. using il-12 in vaccine formulations and combining it with drugs like rifabutin and clarithromycin in mac infections showed improved results, but il-12 can also cause tissue toxicity and autoimmunity, which limits its use.

Ifn-γ is another key cytokine involved in tb immunity. although older studies suggested that ifn-γ might make macrophages more susceptible to tb, later studies showed positive effects, such as faster recovery in mdr-tb patients when ifn-γ was given in aerosol form. giving ifn-γ along with anti-mac drugs improved bacterial clearance in mac and aids co-infected patients. differences in tb susceptibility among populations have also been linked to genetic variations in the ifn-γ gene. tnf-α is another important pro-inflammatory cytokine that activates macrophages to produce nitric oxide synthase-2, which helps kill intracellular mtb. mice lacking tnf-α or its receptor are more vulnerable to tb, and humans taking infliximab, a drug that blocks tnf-α, also have increased risk

of tb. in contrast, il-10 acts as an immunosuppressive cytokine and pushes the immune system towards a th2 response, which is less effective against tb. mtb-infected macrophages produce more il-10, which suppresses il-12 and weakens intracellular killing. blocking the il-10 receptor improves th1 response and helps in better control of infection in both animal and human studies.

Cytokine-based treatment sounds promising, but these cytokines are expensive and can cause serious side effects, which makes them difficult to use in tb-affected, resource-poor countries. therefore, researchers are exploring simple and cheaper immune-modulating chemicals like atp, picolinic acid, imidazoquinolinone, calcitriol, mao-bushi-saishin-to, heat-killed mycobacterium vacate, vitamin d and glutathione. vitamin d has long been known to help tb patients, even in the pre-antibiotic era when sunlight and cod liver oil were used. vitamin d may help by activating tolllike receptor pathways and increasing catholicising, an antimicrobial peptide that kills bacteria. glutathione (gsh), a natural antioxidant in the body, protects cells and also influences whether the immune response becomes th1 or th2. low gsh levels shift the immune system towards th2, which is harmful in tb. tb patients have lower gsh levels, and gsh helps carry nitric oxide (as gsno), which kills mtb. blocking gsh production increases bacterial growth, while increasing gsh using n-acetyl cysteine reduces mtb growth in macrophages. these findings suggest that gsh may have a positive role in tb treatment, but more research is needed.

11.THE RATIONALE FOR THE DEVELOPMENT OF A NOVEL FIXED DOSE COMBINATION ANTI-TB DRUG DELIVERY SYSTEM: - [7]

The development of a new fixed-dose combination (fdc) anti-tb drug delivery system is important because drug delivery today focuses not only on the drug itself, but also on the carrier, route, and target site. modern drug delivery systems aim to improve drug action by controlled or modified release, better bioavailability, improved patient compliance, and a higher therapeutic effect. according to flynn, drug delivery involves using any chemical or mechanical method to control how fast a drug enters the body or reaches the specific tissues where it is needed. this idea has encouraged scientists to redesign old drugs, such as anti-tb drugs, into new dosage forms using advanced delivery methods. one of the biggest problems in tb treatment is that patients often do not take medicines regularly, which leads to treatment failure, complications, and even death. therefore, there is a strong need for an oral anti-tb drug delivery system that can improve the release, breakdown, and targeting of the drugs. from a global health point of view, developing inexpensive, effective, easy-to-take, multi-drug oral formulations with better bioavailability is very important, especially for developing countries where access to doctors and sterile equipment is limited. an oral fixed-dose combination that improves bioavailability and allows patients to safely treat themselves can greatly improve compliance.

The oral route is preferred because it is convenient, comfortable, and safer compared to injections. if overdosing happens, the unabsorbed drug can be removed from the stomach. a once-daily oral anti-tb formulation would greatly improve patient compliance. to improve oral bioavailability, chemical modification or prodrug formation of rifampicin (rif) and isoniazid (inh) may help. prodrugs often increase lipophilicity by masking polar groups, improving absorption. rif was

developed through chemical modification of natural rifamycin's and became clinically useful in 1968, but until now no version of rif has shown major improvement in oral bioavailability. a piperine-containing formulation (piperine improves absorption) increased rif, inh, and pyrazinamide levels in volunteers, but the cost is too high for developing countries. inh, originally synthesized in 1912 and found to have anti-tb properties in 1945, is already a prodrug activated inside mycobacteria. researchers have tried many chemical modifications to improve its pharmacokinetics. some prodrugs increase lipophilicity, some help with membrane permeation and others like inhms provide sustained delivery into macrophages when loaded into microparticles.

Multiarticulate oral systems like microparticles, nanoparticles, pellets, beads, and granules are becoming popular because they offer predictable drug release, better movement through the gastrointestinal tract, fewer side effects, and improved patient acceptance. these systems are especially useful for targeting specific sites in the gut. to make an oral system affordable for developing countries, commonly available polymers and excipients can be used to separate the release of the two drugs. current research is focused on making a rif-inh multiarticulate system that provides different release patterns in the gi tract. studies show that rif needs to be released in the stomach (acidic environment) to ensure good absorption, while inh should be released in the small intestine. the goal is a multiarticulate formulation that gives fast gastric release of rif and targeted intestinal release of inh, improving both bioavailability and treatment effectiveness.

12.CONCLUSION: -

In tb treatment, doctors almost always use a combination of different drugs because the tb bacteria exist in many forms some grow fast, some grow slowly, and some stay dormant. it is very difficult for a single drug to kill all these groups at the same time. among the first-line drugs, only pyrazinamide can kill the slow-growing bacteria well. the current first-line treatment is still the best option we have. however, developing new treatment plans is very important because tb is still the leading cause of death from a single infectious disease. there are many challenges in creating new tb drugs. first, there is no perfect animal model that behaves exactly like human tb. mice are mostly used, but they do not show the same type of disease, do not form must be given caseous granulomas, and cannot mimic latent tb reactivation seen in humans. second, scientists do not fully understand how tb bacteria survive during the latent stage, and no model can fully copy this stage. third, developing a new drug requires huge money (about $800 million to $1.7 billion) and many years, and strict rules make companies less interested in investing. since tb mostly affects poor countries, pharmaceutical companies were less motivated in the past, but recently nonprofit groups have helped increase tb research. another difficulty is testing a new drug when it along with many other drugs. globally, around 16 billion us dollars are needed every year to fight tb. if particle-based drug delivery or immunomodulators can improve treatment, these approaches are worth exploring. better patient compliance can help stop drug-resistant tb by killing bacteria early.

discovering new tb drug regimens, using either new medicines or improved versions of existing ones, could greatly change and improve the worldwide situation of TB.

13.REFERENCES: -

1.THOMAS E. DOBBS1 And RISA M. WEBB2, Chemotherapy of Tuberculosis, 1Mississippi State Department of Health, University of Mississippi Medical Center, Jackson, MS 39215; 2Division Of Infectious Disease, University of Mississippi Medical Centre, Mississippi State Department of Health, G. V. "Sonny" Montgomery VA Medical Centre, Jackson, MS 39216

2.Lisa Claire Du Toit, Viness Pillay* And Michael Paul Danckwerts, Tuberculosis Chemotherapy: Current Drug Delivery Approaches**,** Address: University of the Witwatersrand, Faculty of Health Sciences, Department of Pharmacy and Pharmacology, 7 York Road, Parktown, 2193, South Africa
Email: Lisa Claire Du Toit -Lisad@Worldonline.Co.Za; Viness Pillay - Viness.Pillay@Wits.Ac.Za.

3.Susmita Sarkar, Mavanur R. Suresh, An Overview of Tuberculosis Chemotherapy – A Literature Review, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada. Received, January 24, 2011; Revised, March 23, 2011; Accepted, April 18, 2011; Published, April 18, 2011.

4. Martin Kufa, Vladimir Finger, Ondrej Kovar, Ondrej Soukup, Carilyn Torruellas, Jaroslav Roh, Jan Korabecny, Revolutionizing Tuberculosis Treatment: Breakthroughs, Challenges, And Hope on the Horizon A Faculty of Pharmacy in Hradec Kralove´, Charles University, Hradec Kralove 50003, Czech Republic Biomedical Research Center, University Hospital Hradec Kralove, Hradec Kralove 50003, Czech Republic C.U.S. Army CCDC Chemical Biological Center, MD 210105424, USA Received 28 August 2024; Received in Revised Form 30 October 2024; Accepted 25 November 2024.

5.Jyotsna M. Joshi, Tuberculosis Chemotherapy in the 21st Century: Back to The Basics, Department of Respiratory Medicine, TN Medical College, BYL Nair Hospital, Mumbai, India.

6. Table no.01https://gramproject.com/wp-content/uploads/2020/10/Drugs-for-TB.png

7. Figure no.01(https://www.frontiersin.org/files/Articles/749945/fphar-12-749945-HTML/image_m/fphar-12-749945-g001.jpg)

8.Figure no.02((https://www.frontiersin.org/files/Articles/749945/fphar-12-749945-HTML/image_m/fphar-12-749945-g001.jpg))

9.Figure no.03(https://ars.els-cdn.com/content/image/1-s2.0-S2211383525000292-gr1.jpg)

10.Figure no. 04 https://ars.els-cdn.com/content/image/1-s2.0-S2352396422001128-gr1.jpg