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AN OVERVIEW OF TUBERCULOSIS AND MODE OF ACTION OF ANTI-TUBERCULAR DRUGS WITH THEIR APPLICATION

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ABSTRACT: Tuberculosis is a very serious infectious disease that can lead to death if the person does not take medicine on time. This disease can be spread easily, but it is not mandatory that tuberculosis bacteria will attack suddenly. Still, when the immunity decreases for other reasons, then it will be an attack on health. Before this century, tuberculosis was known as a non-treated disease, but now most drugs are available for treating and curing tuberculosis. This present review provides an overview of the disease and the treatment of tuberculosis.

INTRODUCTION: Tuberculosis (TB) is a contagious infection that is a main causative agent for decreased health and one of the most death causative infections of worldwide. Until the covid-19 pandemic, TB is the most death causes disease from a single infectious agent, after HIV/AIDS [1].

Causative Agent and Prevention of Disease: "Sleep simply and eat nutritious food", this advice was given to patients infected with tuberculosis (TB) in the 1800s, or formerly known as consumption. The airborne disease usually affects the lungs, leading to a severe cough, fever, and chest pain. The disease is spread when a person with TB expels the bacteria into the air. Tuberculosis aerosol infection with USA in tuberculosis the majority of infections produced occur in a single site of infection in the lobe of the lung [2].

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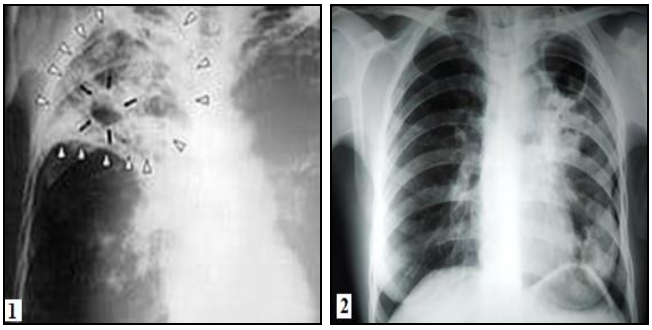

FIG. 1 AND 2: AFFECTED LUNGS

This mysterious disease has a Latin origin that explains the rod shape of the bacillus. German microbiologist Robert Koch discovered the bacterium Mycobacterium tuberculosis that causes tuberculosis in 1882. According to WHO, we can say that almost a quarter of the world's population is currently infected with active TB disease. Active or latent, with over 10 million TB infections and 1.2 million deaths recovered yearly. Reduced access to TB diagnosis and treatment has led to increased TB deaths. The best prediction for 2020 is 1.3 million TB deaths found in HIV-negative people (up from 1.2 million in 2019). 214,000 more people were living with HIV (from 209,000 in 2019), with the total back to 2017 levels.

The reduction in TB incidence (the number of people who develop TB each year) achieved in previous years has slowed by almost half. The impacts will be much worse in 2021 and 2022 [1-3].

Symptoms:

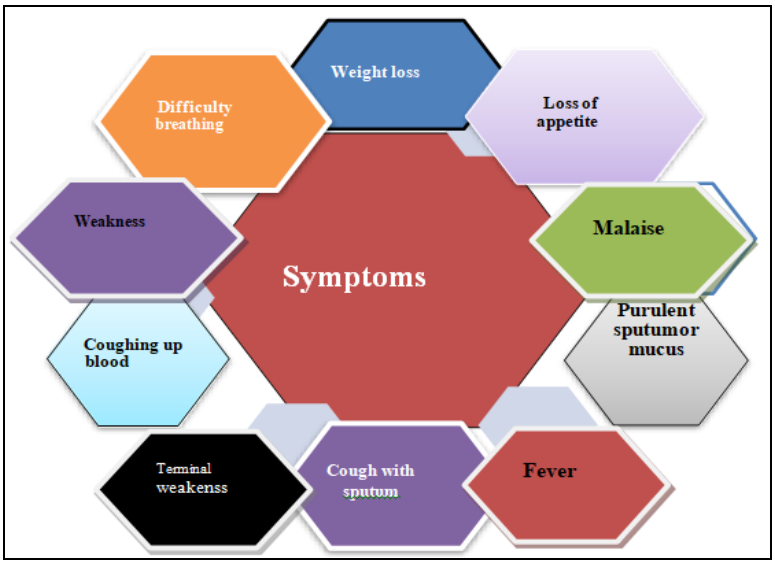

FIG. 3: THESE ARE COMMON SYMPTOMS OF PULMONARY TUBERCULOSIS [4]

Diagnosis and Prevention: The individual and remedial tools demanded to combat the disorder are largely outdated, and disorder prevention and control strategies have been developed, including the DOTS (Short Course on Treatment) program. Directly observed) in 1993, adding the DOTS-plus program to control MDR- TB. (MDR) in 1998. By 2005, 187 countries had started enforcing DOTS and 4.9 million TB cases had been treated with DOTS, this time alone.(5) WHO has linked 5 crucial components of DOTS.

1. The government is committed to supporting TB control conditioning.
2. Case discovery by sputum microscopy in characteristic cases.
3. The 6- to 8- month treatment regimen was formalized for, 444 verified sputum smear-positive cases, with DOTS in the first 2 months.
4. A regular or ongoing force of all essential TB drugs.
5. A standardized recording and reporting system that allows the assessment of TB treatment.

Tuberculosis is the leading cause of death in patients with HIV and pulmonary tuberculosis. People born abroad and those living in poor areas or where malnutrition is common are more infected. The host's own interleukin (IL)-12 deficiency that promotes a helper T- cell (Th) response may be another susceptibility factor for infection. Other conditions may predispose to a higher risk of MTB infection, such as diabetes, aging, prolonged corticosteroid use, TNF-α inhibitors, vitamin D receptor polymorphisms, and IL polymorphisms –twelfth [2]. Since most people with TB are potentially infectious, the development of new diagnostic and screening tools has become necessary to control the disease.

Identification Test of Tuberculosis:

1. Interferon-gamma release test (IGRA)
2. TB skin test (TST)
3. **Interferon-gamma Release Assays (IGRAS):** Detecting active to latent TB by identifying risk factors associated with high and low-burden countries will contribute to developing diagnostic tools and improving our understanding of the immune response in tuberculosis. IGRA is the most sensitive and specific diagnostic test; however, they are expensive and technical. They detected the release of the cytokine IFN-g by T cells that respond to antigens not found in the BCG

vaccine. A blood sample is taken from an individual and IFN-g release is measured.

In Canada and some European countries, it is even suggested to use IGRA and TST together to diagnose ITL, but these tests are not definitive [2].

Tuberculin Skin Test (TST): In the tuberculin skin test (TST), a mixture of tuberculin purified protein derivatives (PPD) of tuberculous proteins injected intradermally into a person caused a delayed type IV hypersensitivity skin reaction. Suppose the individual has been exposed to the mycobacterial proteins in the vaccine or has ever been exposed to a mycobacterial infection. In that case, the size of the skin reaction is measured to identify the person infected with tuberculosis.

The usual standard is from 48 to 72 hours and cut -0.74 to 5 mm -0.40 to 15 mm. However, TST is known to cause false-positive reactions in BCG-vaccinated individuals and false-negative reactions in immune compromised individuals [2].

Some Tuberculosis Diagnosis Approval Tests:

TABLE 1: TUBERCULOSIS DIAGNOSIS APPROVAL [6]

S. no.	Modality	Example	Speed of Detection
1.	Smear microscopy	Ziehl-Neelsen, Auramine	Rapid
2.	Traditional solid cultureon egg-based media	Ogawa, Lowenstein-Jensen	Slow
3.	Modern culture on syntheticMedia	BACTEC MGIT, thin-layer agar	Intermediate
4.	MODS	In-house protocol, Hardy kit	Intermediate
5.	Line probe	INNO-Lipari, MTBDR	Rapid
6.	LAM	TB ELISA	Rapid
7.	NAAT	Amplicon, Gen-Probe,LAMP, GeneXpert	Rapid

Anti-Tuberculosis Agent or Drugs: Anti-tuberculosis agents or drugs used for the treatment or inhibit the growth of mycobacterium tuberculosis known as anti-tubercular agent or drugs.

Classification of Anti-tuberculosis Drugs: Based on a meta-analysis, the World Health Organization (WHO) recently updated its classification of new anti-tuberculosis (TB) drugs.
Anti-TB drug classification is important because it helps clinicians develop appropriate anti-TB regimens for multidrug-resistant (MDR) and widespread drug-resistant (XDR) TB cases.

Does not meet the criteria for a shorter MDR. - TB diet. In previous WHO guidelines (2011), drug selection was based on efficacy and toxicity sequentially from group 1 to group 5.

Group 1 consisted of first-line drugs, and groups 2 to 5 included drugs. Monday Group 5 includes drugs with potentially limited efficacy or limited clinical evidence [7-8].

TABLE 2: WHO 2011 TB DRUGS CLASSIFICATION

S. no.	Group	Therapy/Routes of Drugs	Name of Drugs or Agent
1.	Group1	**First-line oral anti-TB drugs**	Isoniazid Rifampicin Ethambutol Pyrazinamide streptomycin
2.	Group 2	Injectable anti-TB drugs (injectable or parenteral agents)	Kanamycin Amikacin Capreomycin
3.	Group 3	Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin Ofloxacin
4.	Group 4	Oral bacteriostatic Second-line anti-TB drugs	Ethionamide protionamide Cycloserine Terizidone, P-Amino salicylic acid

According to the new WHO medicine class (2016), rifampicin-resistant or multidrug-resistant TB cases should be treated with at least 5 effective anti-TB medicines in the promoter phase pyrazinamide and 4 alternate- line anti-TB medicines. Each medicine is in Group A and B, and at least two medicines are in Group-C. However, one medicine from Group D2 and the other medicines from Group D3 is also needed to bring the aggregate to five if the number of lower effective anti-TB medicines cannot be dialed. However, if pyrazinamide cannot be used, the regimen can be corroborated with class C or D medicines.

Group 1: First-line medicines should be included, isoniazid, rifampin, and pyrazinamide as the primary agents, and ethambutol as a companion medicine. High-cure isoniazid should be added to the TB MDR/ XDR authority when the katG mutation isn't detected by the Genotype study but isn't counted as one of the four active medicines. Pyrazinamide should always be used; although its medicine susceptibility testing is unreliable, it should also not be considered one of the four active medicines. Streptomycin isn't used regularly [8].

Group 2: Injections are included. Kanamycin, amikacin, and Capreomycin are the main medicines [7].

Group 3: The group of medicines called fluoroquinolones are included. Levofloxacin, Moxifloxacin, and Gatifloxacin are the introductory medicines [7].

Group 4: The group of medicines called Oral bacteriostatic Alternate- lineanti- TB medicines include Ethionamide, Protionamide, Cycloserine, Terizidone, P- Amino salicylic acid.

Group 5: This group of medicines known as medicines used in resistant TB Anti-TB medicines with limited data on efficacy and long-term safety in the treatment of medicine-resistant TB. Treatment of medicine-resistant TB include to some medicine as like.

1. Linezolid
2. Clofazimine
3. Amoxicillin
4. Clavulanate
5. Imipenem
6. Cilastatin
7. Meropenem
8. High-doseisoniazid,
9. Thioacetazone
10. Clarithromycin

TABLE 3: WHO 2016 TB DRUGS CLASSIFICATION

S. no.	Groups	Class	Name-of-Drugs
1.	Group A	Fluoroquinolones	Levofloxacin, gatifloxacin Moxifloxacin
2.	Group B	Second-line injectable agents	Amikacin, Capreomycin, Kanamycin (Streptomycin)
3.	Group C	Other core second-line agents	Ethionamide prothionamide, Cycloserine terizidone
4.	Group D	D1	Linezolid
		D2	Clofazimne
		D3	Bedaquiline, Delamanid, P-Aminosalicylicacid, Imipenem–cilastatin, Meropenem, Amoxicillin–clavulanate, (Thioacetazone)

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First Line Anti-Tb Drugs:

Isoniazid: Isoniazid (INH) is effective in acidic and basic media and kills tuberculosis in multiplying organisms. Isoniazid treats tuberculosis or latent TB infection as monotherapy or as part of combination therapy. Less commonly, INH may be used as part of combination therapy for non-tuberculous bacterial infections [8].

INH is completely absorbed orally and penetrates all tissues of the body. Isoniazid is metabolized by acetylation by the hepatic enzyme N acetyltransferase. INH is bio-transformed to nicotinic acid and mono-acetyl hydrazine. Mono-acetyl hydrazine is produced by hepatotoxicity by forming the N-hydroxylated reactive intermediate by the CYP450 mixed oxidation system. The rate of acetylation is genetically determined by slow acetylators characterized by a relative deficiency of N- acetyltransferase in the liver.

Mode of Action: Isoniazid is a prodrug and is actuated by bacterial catalase. Specific activation involves the reduction of mycobacteria ferric catalase- peroxidase KatG by hydrazine and reaction with oxygen to form an oxyferrous enzyme complex. When INH is actuated, it inhibits the synthesis of mycolic acids. Mycolic acid is an essential element of bacterial cell walls. At the remedial position, isoniazid is a bactericidal agent active against the actively growing intracellular and extracellular organisms Mycobacterium tuberculosis [9]. This would demonstrate that INH is formerly an optimal substrate for KatG to convert into species similar as this isonicotinoyl half, and therefore a presumptive pathway for INH- related medicine development could include. The inventors produce isonicotinoyl revolutionaries, independent of KatG, to treat KatG mutant medicine-resistant tuberculosis, although it can be delicate to produce enough mycobacterial spice. Screen of molecules that increase microbial situations of NAD or NADP for use in concurrent use with INH, to maximize product of INH- NAD (P) supplements from amounts limited isonicotinoyl revolutionaries generated in variants similar as S315T. Using the structure of INH- NAD(P) complement products to mastermind more medicine- suchlike motes that specifically inhibit bacterial enzymes similar as InhA or DHFR and develop arylamine N-acetyltransferase inhibitors, a bacterial enzyme that can inactivate INH and may be involved in resistance [9].

Interactions of Isoniazid with Other Drugs:

- Metabolizes para-amino salicylic acid (PAS) INH and prolongs its half-life.
- Albumin hydroxide Antacids and fluoroquinolones inhibit the absorption of INH
- Isoniazid may decrease the abacavir excretion rate, possibly leading to increased serum concentrations.
- Isoniazid may increase the hepatotoxic activity of paracetamol.
- Vitamin B6 (pyridoxine) must be taken in combination with isoniazid to prevent its deficiency.
- Avoid alcoholic beverages such as unpasteurized beer, unless authorized by your doctor, as they may contain tyramine. Drinking

alcohol can increase the risk of isoniazid hepatitis and neurological disease.

- Avoid foods and supplements containing histamine such as skipjack, tuna, and other tropical fish that can cause headaches, sweating, palpitations, flushing and low blood pressure.

Adverse Drug Reaction:

1. Peripheral neuropathy: Due to changes in the use and increased elimination of pyridoxine.
2. Hepatitis: seen in elderly alcoholics with nausea, vomiting, loss of appetite, jaundice.
3. Central nervous system toxicity: Causes psychotic episodes.
4. Other: Anorexia, gastrointestinal discomfort, fever, allergies.

Rifampicin: Rifampicin is a semi-synthetic derivative of rifampicin B obtained from Mediterranean streptococci. Rifampicin is bactericidal against M. tuberculosis and M. laprae. It also inhibits gram-positive and gram-negative bacteria such as staphylococcus, N. meningitis, *H. influenza, E. coli, Klebsiella, premium Pseudomonas* and *legionella* [10].

Rifampicin is a polyketide of the chemical group of compounds known as annamycins, so named because of their heterocyclic structure containing a naphthoquinone ring elongated by a fatty Ansa chain. The naphthoquinone color group gives rifampicin its characteristic orange-red crystal color. Rifampicin is readily absorbed from the gastrointestinal tract. The ester functional group is rapidly hydrolyzed in bile and it is catalyzed by esterase's with high pH and specific substrates, after about 6 hours almost all the drug is defatted. Even in its defatted form, rifampicin is still a potent antibiotic, it can no longer be reabsorbed by the intestines and eliminated from the body [11].

The half-life of rifampicin may be 1.5-5.0 hours, although hepatic impairment is significantly increased. Consuming food inhibits its absorption from the gastrointestinal tract and the drug is eliminated more rapidly; when rifampicin is administered with meals, its maximum plasma concentration is reduced by 36%. Antacids do not affect their absorption. Decreased absorption of rifampin with food is sometimes sufficient to affect the color of urine, which can indicate whether a dose has actually been absorbed [12]. The drug is highly distributed throughout the body and reaches effective concentrations in many organs and body fluids, including cerebrospinal fluid. Since the substance is red, this high distribution is responsible for the orange-red color of saliva, tears, sweat, urine, and the face. Approximately 60% to 90% of the drug is bound to plasma proteins [13-14].

Mode of Action: Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA- dependent RNA polymerase. Crystal structure and biochemical data show that rifampin binds to the β subunit pocket of RNA polymerase in the DNA/RNA channel, but away from the active site. Inhibitors inhibit RNA synthesis by blocking elongation and blocking bacterial host protein synthesis. This steric occlusion mechanism prevents the synthesis of the second or third phosphodiester bonds between the backbone nucleotides of RNA [15].

Prevents elongation of the first year of RNA transcription beyond 2 or 3 nucleotides.

- Rifampicin cannot bind human RNA polymerase (selectively).
- It travels to the cavity, takes in the matter and penetrates the small hole.

Resistance due to DNA mutations and +RNA polymerase mutations affect the binding of rifampin to RNA polymerase. Mycobacteria resistant to rifampicin may occur alone or in combination with resistance to other leading anti-TB drugs. Early detection of widespread multidrug-resistant or drug-resistant TB is key to improving patient outcomes by establishing precise second-line treatments 4044, 4044 and 4044, reducing TB transmission 4044 drug resistance. Traditional methods of detecting resistance involve culturing the bacteria and testing for drug susceptibility, which can take up to 6 weeks.

The Xpert MTB/RIF test is an automated test that detects rifampin resistance and diagnoses tuberculosis. An updated Cochrane review in 2014

indicated that for the detection of rifampicin resistance, Xpert MTB/RIF was accurate, *i.e*. sensitive (95%) and specific (98%) [15-17].

Interaction of Rifampicin with Other Drugs: Rifampicin is the strongest known inducer of the hepatic cytochrome P450 enzyme system, including CYP2B6, CYP2C8, CYP2C9, CYP3C19, CYP3A4CYP3A7, CYP3A9, *etc*. It increases the metabolism of many drugs, making them less effective or ineffective, reducing their effectiveness Levels. For example, patients on long-term anticoagulation therapy with warfarin should have their warfarin dose increased and their clotting time checked frequently because insufficient anticoagulation can lead to serious thromboembolic consequences.

Rifampicin may decrease the effectiveness of oral contraceptives or other hormonal contraceptives by inducing its CYP450 system, as unintended pregnancy has occurred in women who use oral contraceptives and have had very short courses of rifampicin (eg, as prophylaxis against bacterial meningitis). Other interactions include decreased levels and lower efficacy of antiviral drugs, atorvastatin pioglitazone, rosiglitazone, celecoxib, clarithromycin, caspofungin and lorazepam, *etc*. Rifampicin antagonizes the microbiological effects of gentamicin and amikacin. The activity of rifampicin against mycobacterial species can be enhanced by isoniazid (by inhibiting mycolic synthesis) and ambroxol (by host-directed effects on autophagy and pharmacokinetics) [18-20].

Adverse Drug Reaction:

1. **Hepatotoxicity:** (liver failure in severe cases) in patients who drink alcohol or drugs that are toxic to the liver.
2. **Respiratory:** difficulty breathing.
3. **Skin:** flushing, itching, rash, hyperpigmentation,] red and watery eyes.
4. Digestive disorders: nausea, vomiting, diarrhea, abdominal pain.
5. **Flu:** like symptoms such as chills, fever, headache, body aches. Rifampicin penetrates well into the blood-brain barrier, which may directly explain some discomfort and dyspnea in a small number of patients.
6. **Allergic reaction:** skin rash, itching, swelling of the tongue or throat, severe dizziness, and trouble breathing [20-24].

Pyrazinamide (PZA): Pyrazinamide (PZA) is an analogue of nicotinamide, chemically similar to INH but with a weaker effect than INH. Its anti-tuberculosis effect was recognized in 1952. The discovery of PZA as an anti-tuberculosis drug was based on the fortuitous observation that nicotinamide had some activity against mycobacteria [25]. Typically, the synthesis of nicotinamide analogs and direct examination in a mouse model of tuberculosis (TB) infection without *in-vitro* examine have supported the identification of PZA as a more active agent. Before the 1970s, PZA was mainly used as a second-line anti-TB drug to treat drug- resistant tuberculosis or recurrent tuberculosis caused by hepatotoxicity caused by higher doses of PZA and longer duration of treatment.

Used in previous clinical studies. It is more active in acidic media (ph. 5.5) so it is more useful because the tubercle bacilli are present in the phagosomes of the microphage where the ph is present Acidic [26-27]. Pyrazinamide is very effective during the first two months of treatment. Pyrazinamide is combined with other medicines and must not be used alone. Pyrazinamide is well absorbed orally and has good penetration into the cerebrospinal fluid. Currently, pyrazinamide is considered safe during pregnancy [28].

Mode of Action: PZA is a prodrug converted to its active metabolite pyrazonic acid by a pyrazinamide enzyme in the bacillus. pyrazonic acid interacts with fatty acids and inhibits mycolic acid synthesis. Alpha-branched mycolic acid; long-chain beta hydroxy fatty acids found in the cell wall of M. tuberculosis [29-32].

Adverse Drug Reaction:

1. Hepatotoxicity is most common adverse effect
2. Hyperuricemia
3. Abdominal disturbance
4. Flushing, rashes, and fever *etc*

Ethambutol (EMB): Ethambutol is used in the management and treatment of tuberculosis. This is a bacteriostatic drug, which inhibits cell wall synthesis. EMB has been available to treat tuberculosis since the 1960s. The original formulation of EMB contained a raxemic mixture of the L and D forms. The D form of ethambutol is known for its therapeutic activity, however, L is known. Was toxic and therefore discontinued. Ethambutol is used to treat pulmonary tuberculosis. It should not be used alone, but with at least one other anti-tuberculosis drug such as isoniazid. EMB is effective against strains of the bacterium Mycobacterium tuberculosis but not against viruses, fungi, or other bacteria. Anti-tuberculosis drugs used with EMB include cycloserine, ethionamide, pyrazinamide, viomycin, isoniazid, aminosalicylic acid, and streptomycin [33]. Ethambutol should not be used alone for initial or reliever treatment. It should be used together with another anti-tuberculosis drug. Current first-line treatment for TB is a quadruple treatment of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) for 2 months, followed by a 4-month continuation of isoniazid and rifampicin and/or ethambutol [34].

Mode of Action: Ethambutol is first-line tuberculosis (TB) treatment. Ethambutol is considered a bacteriostatic drug, interfering with arabinogalactan biosynthesis interfering with mycolic acid for cell wall synthesis. The researchers state that ethambutol has a synergistic effect with isoniazid (INH) against Mycobacterium tuberculosis through a mechanism of transcriptional repression of the Inh-A gene, a gene targeted by INH that encodes the reductase enzyme carrying enoyl-acyl, which is required for bacterial cell wall integrity. One study indicated that ethambutol bound to the transcriptionally regulated Tet R increased the inh-A gene's sensitivity to INH. Thus, it increases the destructive effect of INH [35-36].

Adverse Drug Reaction:

1. Optic neuropathy/optic neuritis/retrobulbar neuritis
2. Decreased visual acuity
3. Scotoma
4. Color blindness
5. Visual defect (e.g., blurred vision)
6. Peripheral neuropathy
7. Hepatotoxicity
8. Numbness and tingling of extremities due to peripheral neuritis
9. Mental confusion, disorientation, and possible hallucinations
10. Psychosis
11. Other effects - nausea, vomiting, fever, rashes, *etc* [37-41].

Streptomycin: Streptomycin is the first-line anti-tuberculosis drug. Streptomycin is an aminoglycoside antibiotic and was isolated from the bacterium Streptomyces griseus. And Effective Tuberculosis Treatments Used Today are mainly used as part of a multi-drug treatment for pulmonary tuberculosis. It has additional activity against gram-negative aerobic bacteria such as brucellosis, malaria, and plague (Y. pestis). This activity discusses the indications, mechanism of action, and contraindications for streptomycin use in children and adults [42-43]. It is used in combination with isoniazid, pyrazinamide, and rifampin. The use of streptomycin is being embraced in the emerging discussion of treating drug-resistant Mycobacterium tuberculosis infections, where the standard combination therapy of rifampin, d isoniazid, pyrazinamide and ethambutol were ineffective. Therefore, streptomycin is considered an acceptable alternative therapy among other selected antibiotics with activity against M. tuberculosis (rifapentine, rifabutin, linezolid, and some fluoroquinolone antibiotics such as Levofloxacin, gatifloxacin, *etc*.) and moxifloxacin.) Streptomycin is poorly absorbed from the gastrointestinal tract and is usually administered by intramuscular and deep intravenous injection. The half-life of streptomycin is approximately 2.5 hours [44-45].

Mode of Action: Streptomycin has a bactericidal effect and interferes with ribosomal peptide/protein synthesis. It binds to one side of the 16S rRNA located on the smaller 30S component of the bacterial ribosome, inhibiting function and stopping protein synthesis by inhibiting peptide bond formation. Aminoglycosides are hydrophilic, *i.e*.

they cannot penetrate the hydrophobic membrane of bacterial cells. The cellular respiratory cycle requires An electron transport system to achieve this [46-48].

Adverse Drug Reaction:

1. Hypokalemia with long-term treatment, convulsions
2. Encephalopathy in severe cases.
3. Streptomycin has a loose association with immuno-allergic hemolytic anemia.
4. Streptomycin is contraindicated in patients with known renal impairment,
5. Streptomycin is contraindicated during pregnancy due to its ability to cross the placenta combined with its known ototoxic effects [49, 50].

Second Line Anti-Tb Drugs:

Linezolid: Linezolid is a basic oral drug with bactericidal and antiseptic effects. Evidence of good efficacy is accumulating, including meta-analyses, two RCTs, and observational studies. Unfortunately, its current cost and documented toxicity may be barriers to its wider use.

The price of quality-assured generic linezolid has dropped significantly over the past year, and global costs are expected to fall further soon. Regarding toxicity, reducing the initial dose of linezolid or adjusting the dose during treatment has shown an improvement in tolerability without affecting its efficacy. Indeed, adverse events are less likely with the use of linezolid 300 mg • day -1. CT is a useful and simple tool that is easy to implement [7, 50-52].

Oxazolidinones: Oxazolidinones, an inhibitor of protein synthesis, is the sole mechanism of action against tuberculosis. The oxazolidine group includes linezolid and sutezolid. *In-vitro*, linezolid was effective at 1-2 µg/mL doses against 90% of clinical isolates and worked well in mouse models.

Unfortunately, long-term use of linezolid has been associated with toxicity, such as neuropathy and myelosuppression. Still, the drug has been evaluated in the treatment of drug-resistant tuberculosis with good results. Clinical trials are planned to investigate linezolid in patients with extensive multidrug-resistant and drug-resistant tuberculosis. [8]

Bedaquiline and Delamanid: Bedaquiline and Delamanid may have the characteristics required to be part of hypothesis group 3, if the promising data available are confirmed and both drugs can be safely prescribed for the entire duration of treatment. Treatment, not just for six months.

Bedaquiline: targets both actively reproducing bacilli and inactive bacilli, thus having the properties required of a basic drug. The available evidence for efficacy and safety includes RCTs and observational studies, including experience from compassionate use programs. Given its efficacy, the first planned phase II controlled trial of bedaquiline reported a faster change in sputum culture in patients receiving bedaquiline compared with controls. % for the placebo group, after 2 months, i.e. 77.6% versus 57.6% at 6 months. At the end of the analysis at 30 months of follow-up, a 58% cure rate occurred in patients receiving bedaquiline compared with 32% for the control group [7]. These adverse events are critical to the WHO recommendations for the use of bedaquiline and for this reason, active surveillance, pharmacovigilance, and good management of adverse events are essential in No. 5 criteria are required to make this drug. Finally, the potential problem is cross-resistance to clofazimine.

Delamanid: can also be considered a basic medicine due to its bactericidal and antiseptic effects. Unlike bedaquiline, it has not shown cross-resistance with other anti-tuberculosis drugs. Several studies and RCTs are notable for its effectiveness, and there are also positive experiences about its compassionate use. In the first published clinical trial of delamanid, conversion of cultures after 2 months was expected to occur in the group receiving the drug compared with the placebo group, while other adverse events were similarly distributed across the three groups for this reason, the WHO recommendation for the use of delamanid including the same five performance criteria as in the case of bedaquiline [8].

Fluoroquinolones: Fluoroquinolones (FQs) are not only very effective antibiotics on TB But also useful in some other disease or infection.

Some fluoroquinolones, like as *i.e.* Moxifloxacin, Gatifloxacin and Levofloxacin, are the most valuable first-line anti-TB agents according to current WHO guidelines. Fluoroquinolones are the newest class of drugs, including ciprofloxacin, ofloxacin, Levofloxacin and sparfloxacin commonly used against Mycobacterium tuberculosis. Fluoroquinolones are generally well tolerated with prolonged use in treating tuberculosis, but serious adverse events have been reported with fluoroquinolones. The most common drug interactions with fluoroquinolones in the treatment of tuberculosis include malabsorption interactions involving multivalent cations and CYP450 interactions with ciprofloxacin. Increased risk of central nervous system" CNS" Adverse events associated with concurrent use of cycloserine have been reported.

Five clinical trials examined treatment outcomes with moxifloxacin, gatifloxacin, and Levofloxacin for pulmonary tuberculosis. In the first clinical trial, moxifloxacin was differentiated from Levofloxacin in treating MDR-TB. In the remaining four clinical trials, the results of the seven fluroquinolone regimens (moxifloxacin: five, gatifloxacin: two) differed from the WHO-recommended standard daily, five times, or three times a week (twice, moxifloxacin: a), gatifloxacin: a) treatment against drug-sensitive tuberculosis, has been published. The three-weekly DS-TB diet is no longer recommended in WHO guidelines. (First) A 4-month regimen containing moxifloxacin or gatifloxacin completely cured 75-90% of patients with pulmonary tuberculosis, but no one reported a beneficial outcome after a follow-up period of nearly 6 months, compared with the standard TB-DS regimen.

Mode of Action: Quinolones have activity against topoisomerase-2 and work by blocking DNA replication and inhibiting cell synthesis and division. Quinolone antibiotics inhibit DNA synthesis by targeting two essential topoisomerase-2, DNA gyrase, and topoisomerase-4. Both targets allow one molecule of double-stranded DNA to pass through another, followed by the disassembly of the original strand, thereby changing the number of DNA bonds by a factor of two at each enzymatic step. Although the two enzymes show a high degree of similarity in their structure and function, their specific DNA replication functions differ. DNA gyrase is an enzyme found only in bacteria and not in humans. This enzyme uses energy from the hydrolysis of ATP to introduce negative superhelices into DNA. This unidirectional supercoil activity is induced by asymmetric coiling of the DNA around the specific region of the enzyme before passage through the strand. Negative DNA supercoiling is required for chromosome compaction, reduces torsional stress during replication, and promotes local fusion for important processes such as transcription initiation by RNA polymerase. DNA gyrase is absent in eukaryotic cells, therefore, is an excellent target for quinolones and is essential for bacterial growth. This enzyme consists of two subunits A and B forming the A2 B2 tetramer.

Adverse Drug Reaction:

- Phototoxicity
- GIT discomfort -nausea, vomiting, abdominal pain and stomach pain
- CNS toxicity

Types of Drug Resistance:

A. Monopoly: This resistance occurs only with first-line anti-TB drugs.

B. Resistance: Resistance occurs to multiple first-line anti-TB drugs, as well as isoniazid and rifampin.

C. Multi-drug Resistance (MDR): at least developed resistance to isoniazid and rifampicin.

D. Rifampicin Resistance (RR): Resistance induced by rifampicin is detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether single-resistance, multi-drug-resistant, multidrug-resistant, or widespread.

E. Extensive drug resistance (XDR): Resistance produced by any fluoroquinolone and at least one of the three second-line injectable drugs capreomycin, kanamycin, and amikacin, including multi-drug resistance [2, 10, 54-55].

Risk Factors for MDR-TB:

1. Absence of response for first line DOTS schema.
2. Recurrence after a full course of treatment with the first regimen.
3. Treatment after stopping TB treatment with first-line regimen. Exposure to a known case of multidrug-resistant tuberculosis.
4. HIV co-infection [54].

Treatment of Drug-Susceptible Tuberculosis: The effective treatment in patients with no suspected resistance is a two-month enhanced HRZE period, followed by a 4-month continuation phase on HR. Ethambutol may be discontinued if sensitivity testing shows that the patient's isolate is susceptible to HR. However, suppose the patient's chest x-ray shows a defect and the culture is still positive at the end of the initial phase. In that case, extending the continuation period for another 3 months is recommended [53].

The bactericidal and sterilizing activity of fluoroquinolones and the ability to shorten current treatment regimens for tuberculosis has been recently evaluated. Shorter 4-month regimens containing FQ (Remox, Oflotub and Rifaquin) were associated with a higher rate of relapse at 18 months of follow-up than the standard 6-month regimen containing rifampicin. However, the regimen 2-month chart has a slightly higher FQ than the culture conversion rate. Therapeutic drug monitoring (TDM) is useful in customizing TB treatment to confirm appropriate coverage or inform clinicians of potentially resistant under-treatment or super-treatment levels. May lead to toxicity. CT is mainly useful in cases of severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption, where drug interactions are likely to occur, and impaired clearance in the kidney [4].

Treatment of Drug-Resistant Tuberculosis: Current guidelines recommend that patients with RR or MDR TB, who are not eligible for shorter regimens, receive at least five active anti-TB drugs in the booster phase, including pyrazinamide and four second-line anti-tuberculosis drug - l 'one is chosen from group A, one from group B and at least two from group C. If the lower effective anti-tuberculosis drug cannot be composed as above, a group D2 and other drugs from class D3 can be added to bring the total to five.

The current WHO-recommended classification for developing treatment regimens for MDR-TB. According to WHO guidelines for MDR-TB, this regimen should, if possible, include pyrazinamide, moxifloxacin, second-line injection, two primary second-line agents (ethionamide or prothionamide, cycloserine, linezolid and/or clofazimine). If the regimen is not possible with the above agents, other complementary agents can be used to develop the regimen, including bedaquiline, the clinician delamanid based on recommended international guidelines [4, 10, 51, 52].

Most effective treatment regimen is the ‘‘Bangladesh’’ standardized regimen, achieved a relapse-free cure of 87.9% among 206 patients with a 9 to 12-month duration of the therapy with Clofazimine, Gatifloxacin, Ethambutol and Pyrazinamide throughout the treatment period and including Prothionamide, Kanamycin and high-dose Isoniazid during intensive phase of a minimum of 4 months, this regimen achieved < 1% failure and 90% relapse-free cure [11].

TABLE 4: TREATMENT STRATEGY FOR TUBERCULOSIS

S. no.	standard	Standard insome developing countries	Mono- resistance torifampicin	Mono- resistance toisoniazid	Multi-drugresistance
1.	Rifampicin, 6-months	Isoniazid, 8-months	Isoniazid, 18-months	Rifampicin, 12 months	Five drugs initially, then tests
2.	Isoniazid, 6-months	Ethambutol, 8-months	Ethambutol or pyrazinamide or both, 18 months	Ethambutol or pyrazinamide, 12months	
3.	Ethambutol, 2-months	Rifampicin, 2-months			
4.	Pyrazinamide 2–months	Pyrazinamide 2-months			

RNTCP (Revised National Tuberculosis Control Program): The revised National Tuberculosis Control Program (RNTCP) provides free diagnostic and therapeutic services to all registered TB patients. In the early 1990s, tuberculosis was shown to decrease as socio-economic conditions improved. In fact, tuberculosis has been convincingly proven to be manageable in all socio-economic situations. According to a new WHO report, the incidence of tuberculosis has decreased by only 2% per year in all six WHO regions. Global collaborative efforts over the last two decades have helped to make remarkable progress in global TB control [54]. Under India's revised National Tuberculosis Control Program (RNTCP), diagnostic and therapeutic services are integrated into the general healthcare system.

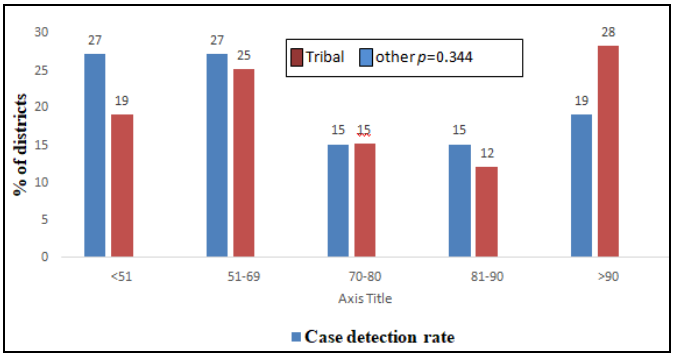

FIG. 4: RNTCP (REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAM

Now, RNTCP is an essential part of the National Rural Health Mission (NRHM). For quality diagnosis, dedicated microscope centers are set up for every 10,000 rupees in the general area and for every 50,000 inhabitants of tribes, hills and difficult areas. A tuberculosis prevalence survey conducted among Saharan tribes showed high prevalence in this population with inadequate access to health services [9, 10]. With equal access prioritizing hard-to-reach groups such as tribal areas, RNTCP has expanded its TB control activities, especially for tribal people [13]. Revised National Tuberculosis Control Programme (RNTCP) was coming into existence by manufacturing and accepting the internationally approaches to Directly Observed Treatment Short course (DOTS) plan as the most systemic and low-cost approach to revitalize the TB control programme in India. To bring out the aim the first objective is to achieve and maintain - a cure rate of at least 85% among new identified infectious (new sputum smear positive) cases and to bring out and maintain identification of at least 70% of such cases in the society. Treatment success rate has been enhance from 25% to 86% from 1998 to 2004. Death rate has been brought decrease seven-folds, from 29% to 4 % [13, 14].

Covid-19 Who Guidance on Pandemics and Tuberculosis: Since, COVID-19 was declared a public health emergency of international concern, the WHO Global TB Program has been monitoring the impact of pandemics on TB services and providing guidance and support to NTP and partners [54-55].

1. It was Leverage NTP's expertise and experience, especially in rapid diagnostics and contact tracing, for COVID-19 responses.
2. Maximize remote care and support for people with tuberculosis by expanding the use of digital technology.
3. Minimize the number of visits to medical services required during treatment, such as the use of WHO-recommended total oral tuberculosis treatment regimens and community-based care.
4. Limit TB and COVID-19 infections in communities and healthcare facilities by ensuring basic infection prevention and management of healthcare professionals and patients,
5. Cough etiquette, and patient triage.
6. We support the provision of TB prevention treatment by building synergies with COVID-19-related contact tracing efforts.
7. Provide individuals with simultaneous TB and COVID-19 testing, including the use of the Tuberculosis Laboratory network and platform, as needed.
8. To ensure proactive planning and budgeting for both conditions (including the catch-up phase), material procurement, and risk management.

Future Strategy of who and United Nation: Strategy and the political declaration of the UN high-G deadline of 2030 level meeting on TB, for the period up to the SD Global TB targets set in the SDGs, the End TB.

TABLE 4: FUTURE STRATEGY FOR TUBERCULOSIS

S. no.	Society	Future Aspects
1.	SDG Target 3.3	From 2030, at least of these epidemics of AIDS, TB, malaria and mistreated tropical infection, and combat hepatitis, water-based infection and other infectious diseases
2.	WHO end TB Strategy	80% decrease in the TB incidence rate (new and repeated cases per one lakhs population per year) from 2030, comparison with 2015 2020 landmark: 20% decrease; 2025landmark: 50% decrease. 90% decrease in the yearly number of TB deaths from 2030, comparisonwith 2015 2020 milestone: 35% decrease;2025 landmark: 75% decrease. Households people was not affecting by TB face catastrophic costs from 2020
3.	UN High-level meeting on TB, 2018	crores population had been treated to TB from 2018 to2022, including: " 0.35 crores children " 0.15 crores Population with drug-resistant TB,including 1lakhs fifteen thousand childs. At least 3 crores population provided with TB preventiveand curative treatment from2018 to 2022, including: "0.6 crores population suffering with HIV " 0.4 crores children which under 5 years aged and 20 million population in some other age groups, which are household contacts of the population affected by TB. Fund will provide at least US$ 1300 crores per year for global access to Tuberculosis prevention, diagnosis, treatment and care by 2022. Fund is providing for at least US$ 200 crores per year for Tuberculosis research from 2018 to2022

CONCLUSION: This present review gives information about an overview of tuberculosis disease, its treatment aspects, and the chance of MDR. This review provides information about anti-tuberculosis drug and their indication and also provide adverse drug reaction detail of anti-tuberculosis drug and provide information about the government, WHO and UN strategy for control program of tuberculosis disease in the world level.

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