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International Journal of Pharmaceutical Chemistry and Analysis

Journal homepage: <https://www.ijpca.org/>

Review Article

Antibiotic drug resistance TB in India

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ARTICLE INFO

Article history:

Received 23-12-2021

Accepted 29-12-2021

Available online 25-01-2022

Keywords:

Tuberculosis

Treatment

Antibiotics

Drug resistance TB in India

ABSTRACT

Tuberculosis is a disease caused by bacteria spread from person to person through air. TB usually affects the lungs, but it can also affect other parts of the body, such as brain or kidney. Global surveillance has shown that drug resistant TB is widespread and is now a treat to tuberculosis control programs in many countries. This review describes treatment of tuberculosis and the drug resistance problem in India.

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1. Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Tuberculosis (TB) remains as an important transmissible disease and public health concern worldwide.¹ According to the latest World Health Organization (WHO) report, there were an approximately 8.6 million cases of TB in 2012 and 1.3 million deaths were occurred by this disease. More than half a million cases happened in children and 320,000 deaths were reported in between HIV-infected persons.¹ However, even more disturbing is the emergence of drug resistance. In 2012, there were an estimated 450,000 cases of multidrug resistant (MDR)-TB and 170,000 deaths were due to it. MDR-TB is caused by strains of *Mycobacterium tuberculosis* that are resistant to at least Rifampicin and Isoniazid, two key drugs in the treatment of the disease. Since 2006, it has been recognized the presence of even more resistant strains of *M. tuberculosis* identify as extensively drug resistant (XDR)-TB.²⁻⁴ These strains in addition to being MDR are also resistant to any fluoroquinolone and to at least one of

the injectable second-line drugs: kanamycin, capreomycin or amikacin. More recently, a more anxious situation has emerged with the description of *M. tuberculosis* strains that have been found resistant to all antibiotics that were available for testing, a situation identify as totally drug resistant (TDR)-TB.⁵⁻⁹

The first antituberculous drug, streptomycin, was identified in 1944.¹⁰ The newly discovered drug was immediately used for treatment of TB patients. The condition of many individual TB patients receiving streptomycin improved during the first months of treatment, only to then worsening again as treatment continued. It was soon understood that this was due to the evolution of resistant *M. tuberculosis* strains, make streptomycin ineffective.¹¹ To limit the evolution of resistance, the British Medical Research Council pioneered the first combination therapy for the treatment of a disease by using para-aminosalicylic acid together with streptomycin for treatment of pulmonary TB.¹² The subsequent years saw the introduction of an array of different antituberculous drugs. The discovery of rifampicin in 1965 and the successive use of the drug in TB treatment was a game changer, allowing dramatically shortened treatment duration from

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18 months or more to 9 months.¹³ During the 1990s, the current standard 6-month regimen known as Directly Observed Therapy Short Course (DOTS) was introduced by the World Health Organization. This regimen consists of 2 months treatment with isoniazid, rifampicin, ethambutol and pyrazinamide followed by 4 months of isoniazid and rifampicin and is highly effective for drug-susceptible T.¹⁴

A short treatment duration and reduction of adverse drug effects are pivotal for increasing patient treatment adherence which is known to influence the evolution of drug resistance.¹⁵ However, in spite of the early establishment of TB combination therapies showing high cure and low relapse rates, drug-resistant *M. tuberculosis* strains continued to develop in both high and low incidence settings. MDR *M. tuberculosis* exception evolved on multiple occasions in different parts of the world. Furthermore, differences in the quality of public health systems contributed to the spread of drug-resistant *M. tuberculosis* variants leading to the unequal distribution of incidence rates of drug-resistant variants around the world we observe today. In the absence of an effective vaccine, there is an urgent need for new treatment process, drugs and diagnostics to slow the evolution of drug resistance and limit transmission of resistant variants, as well as to completely the treatment outcome of patients infected with MDR/XDR *M. tuberculosis* strains. Understanding the molecular mechanisms and the evolutionary trajectory of drug resistance is important to limit the *de novo* evolution and subsequent spread of resistant *M. tuberculosis* strains.¹⁶

The conception of XDR-TB was first introduced at the Centers for Disease Control and Prevention (CDC) in March 2005.¹⁷ Shortly thereafter, the data on resistance to second line drugs (SLDs) were reported during an pandemic outbreak at KwaZulu-Natal, South Africa, resulting in shocking death among TB cases co-infected with HIV in February 2006.¹⁸ The global emergence of XDR-TB has raised the concern that the current existence of mostly drug susceptible TB will be replaced with a complicated form of TB with limited treatment strategies. The emergence of XDR-TB can be prevented by effective management with SLDs in rifampicin-resistant TB (RR-TB) as well as multidrug-resistant TB (MDR-TB) cases. This review aims to focus on the completely management strategies for patients suffering from XDR-TB.

2. Definition

XDR-TB was defined as those TB cases with authenticated resistance to isoniazid (H) and rifampicin[®] and at least three of the six main classes of SLDs [aminoglycosides, polypeptides, fluoroquinolones (FQs), thioamides, cycloserines (Cs) and para-aminosalicylic acid].¹⁹ However, the WHO amended the case definition of XDR-TB as 'TB with resistance to at least H and R as well as further resistance to any FQs [ofloxacin (Ofx), levofloxacin

(Lfx) or moxifloxacin (Mfx)] and second-line injectable drugs (SLIDs) [kanamycin (Km), amikacin (Amk) or capreomycin (Cm)] at an emergency meeting of the Global XDR-TB Task Force. This definition was considered in view of difficulty in testing some SLDs and less treat ability of some forms of drug resistance as compared to others.²⁰ Further, two new terms pre-XDR-TB and extremely drug-resistant TB (XXDR-TB) have been introduced recently based on SLDs resistance patterns. Pre-XDR-TB was defined as a subset of MDR-TB cases that are resistant to either FQ or SLID but not to both, thereby not fulfilling the criteria of XDR-TB. Another term XXDR-TB also known as totally drug-resistant TB (TDR-TB) was suggest for cases resistant to all available first-line drugs and second-line drugs (SLDs).²¹ It was further accredit that these results should not be utilized only to guide treatment as there is still lack of appropriate reproducibility and reliability of drug susceptibility test (DST) for the remaining SLDs as well as standardized strategy for testing.²² There could also be inconsistency as *in vitro* DST results might describe resistance for a particular strain of *Mycobacterium tuberculosis* although there might not be actually any resistance *in vivo* and the anticipating relevance of these results without an internationally accepted and standardized DST would remain unclear.

3. Treatment

Treatment is difficult because the second-line TB drugs are more weak and toxic. The majority of these drugs were developed years ago but very rarely used because of poor side effect profiles. Due to the weak sterilizing activity of the second-line TB drugs, treatment generally takes 18–24 month. In the best treatment programs, which address socioeconomic barriers and assertively manage side effects, cure rates of 60%–80% have been reported worldwide, however, the cure rate for MDR-TB is much lower. In 2013, the WHO reported that only 48% of MDR-TB patients were cured. The overall cure rate for XDR-TB is even lower: Only 20% are cured, and 44% die. Anti-TB drugs commonly divided into first- and second-line anti-TB drug. Isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin being the primary first-line anti-TB drugs, where fluoroquinolones, amikacin, kanamycin, capreomycin, para-amino salicylic acid and cycloserine being the second-line anti-TB drugs.

Duration of drug exposure is different according to the susceptibility of the isolated strains. Generally, two different steps in the treatment of tuberculosis, 1.) initial (or bactericidal) phase and 2.) continuation (or sterilizing) phase. During the first step of treatment, mycobacteria with a high replication rate are killed, and, consequently, with the histological pulmonary restoration and the reduction of the inflammation process, symptoms and clinical signs resolve (clinical recovery). From a public health perspective,

Table 1: Anti-TB drugs and their side effects

Drug	Explanation of drug& dose	Side effects
Isoniazid (H)	Explanation: Bactericidal; inhibits mycolic acid synthesis most effectively in dividing cells; hepatically metabolized. Dose: : 300 mg daily or 900 mg twice or thrice weekly	Common: Hepatitis (10% – 20% have elevated transaminases), peripheral neuropathy (dose-related; increased risk with malnutrition, alcoholism, diabetes, concurrent use of aminoglycosides, or ethionamide). Less common: Gynecomastia, rash, psychosis, seizure.
Rifampicin ®	Explanation: Bactericidal; inhibits protein synthesis by blocking mRNA transcription and synthesis; hepatically metabolized. Dose: rifampicin 600 mg/d; rifabutin 300 mg/d.	Common: Orange-colored bodily secretions, transient transaminitis, hepatitis, gastrointestinal distress. Less common: Cholestatic jaundice.
Ethambutol (E)	Explanation: Bacteriostatic at conventional dosing (15 mg/kg); inhibits lipid and cell wall metabolism; renally excreted. Dose: 15–25 mg/kg	Common: Generally welltolerated. Less common: Optic neuritis gastrointestinal distress, arthritis/ arthralgia
Pyrazinamide (Z)	Explanation: Bactericidal; mechanism unclear; effective in acidic milieu (e.g., cavitary disease, intracellular organisms); hepatically metabolized, renally excreted. Dose: 15–40 mg/kg daily	Common: Arthritis/ arthralgias, hepatotoxicity, hyperuricemia, abdominal distress. Less common: Impaired diabetic control, rash.
Streptomycin(S)	Explanation: bactericidal; protein synthesis inhibitor. Dose: 15 mg	Common: Ototoxicity, nephrotoxicity, neurotoxicity. Less common: Neonatal deafness
Fluoroquinolones Levofloxacin (Lfx) Moxifloxacin (Mfx)	Explanation: Bactericidal; DNA gyrase inhibitor; renally excreted. Dose: levofloxacin 750 –1000 mg/d; moxifloxacin 400 mg/d.	Common: Generally welltolerated, well-absorbed. Less common: Diarrhea, dizziness, gastrointestinal distress, headache, insomnia, photosensitivity, rash, vaginitis, tendonitis, psychosis, seizure (CNS effects seen almost exclusively in elderly).
Amikacin (Amk) Kanamycin (Km) Capreomycin (Cm)	Explanation: Bactericidal; aminoglycosides inhibit protein synthesis through disruption of ribosomal function; less effective in acidic, intracellular environments; polypeptides appear to inhibit translocation of the peptidyl-tRNA and the initiation of protein synthesis; renally excreted. Dose: 15–20 mg/kg daily	Common: Pain at injection site; proteinuria; electrolyte wasting, cochlear ototoxicity. Less common: Nephrotoxicity; peripheral neuropathy; rash; vestibular toxicity.
Para-aminosalicylic acid (PAS)	Explanation: Bacteriostatic; disrupts folic acid metabolism (thought to inhibit the biosynthesis of coenzyme F in the folic acid pathway) hepatic acetylation, renally excreted. Dose: Depends on specific formulation	Common: Gastrointestinal distress (nausea, vomiting, diarrhea); hypersensitivity; hypothyroidism (especially when taken with ethionamide). Less common: Hepatitis, electrolyte abnormalities. Drug Interactions: Decreased isoniazid acetylation; decreased rifampicin absorption in nongranular preparation; decreased vitamin B12 uptake.
Cycloserine (Cs)	Explanation: Bacteriostatic; alanine analog; interferes with cell wall synthesis; Neurologic and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors. Less common: Psychosis, peripheral neuropathy, seizures (increased risk of CNS effects with concurrent use of ethanol, isoniazid, ethionamide, or other centrally acting medications), hypersensitivity	Common: Neurologic and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors. Less common: Psychosis, peripheral neuropathy, seizures (increased risk of CNS effects with concurrent use of ethanol, isoniazid, ethionamide, or other centrally acting medications), hypersensitivity
Ethionamide (Eto)	Explanation: May be bactericidal or bacteriostatic depending on susceptibility and concentrations attained at the infection site; the carbothioamide group, also found on thiacetazone, and the pyridine ring, also found on isoniazid, appear essential for activity; hepatically metabolized, renally excreted. Dose: 500 –1000 mg/d.	Common: Gastrointestinal distress (nausea, vomiting, diarrhea, abdominal pain, loss of appetite); dysgeusia (metallic taste); hypothyroidism (especially when taken with PAS). Less common: Arthralgias, dermatitis, gynecomastia, hepatitis, impotence, peripheral neuropathy, photosensitivity

this phase is crucial because the treated patient becomes noninfectious and the probability of selection of drug-resistant strains decreases (it is directly correlated to the fast-growing bacteria). The continuation phase is oriented to the elimination of semidormant bacteria, whose size is significantly reduced if compared with that at the beginning of the anti tuberculosis therapy; this quantitative feature, related to the low replication rate, is associated with a low probability of emergence of drug-resistant mycobacteria. In cases of drug-susceptible tuberculosis, two potent medicines are sufficient (e.g., isoniazid and rifampicin) in this phase. On the other hand, the regimen prescribed during the initial phase is more complex: two bactericidal drugs (isoniazid with streptomycin or rifampicin), ethambutol to inhibit monoresistant strains and to reduce the mycobacterial burden, and pyrazinamide, whose action is mainly focused to the semidormant mycobacteria. The intensive phase has a duration of 4 month.

3.1. Treatment of HIV and tuberculosis

Patient who have tuberculosis and AIDS raises four key issues. Firstly, patients may fail to properly absorb the anti tuberculosis drugs, which may increase the risk of treatment failure, relapses, and obtained drug resistance. Secondly, drug-drug interactions may compromise antiretroviral and anti tuberculosis treatment, as well as increase the risk of acquired drug resistance and toxicity.^{23,24} People who have both disorders are managed by clinicians who have special experience and interest in this patient population. Because the anti-retroviral drugs are less readily available in most developing countries than in the developed world, treatment of tuberculosis in people with AIDS as suggested by the US Centers for Disease Control and Prevention is not possible in many countries. Thirdly, because antiretroviral therapy reestablished CD4 lymphocyte numbers and immune function, patients may experience a paradoxical worsening of symptoms or other manifestations—for example, worsening of infiltrates on chest radiographs, enlarging pleural or pericardial effusions, swelling on lymph nodes—from pre-existing infections including tuberculosis.^{25,26} Delaying the initiation of antiretroviral therapy until the patient has completed several months of tuberculosis treatment reduces the risk and severity of such reactions but does not totally obviate the hazards. Fourthly, patients seem to have a moderately increased risk of relapse. Despite this, the 1994 guidelines of the US Centers for Disease Control and Prevention and the American Thoracic Society recommended the standard six month regimen, with the caveat that treatment should be prolonged in “slow responders.”

3.2. Treatment of tuberculosis and diabetes

In insulin-dependent patients, it is recommended that the RHZE(R-rifampin,H- isoniazid,Z-pyrazinamide,E-ethambutol) regimen be extended for 9 months. In non-insulin dependent patients, the regimen remains uniform, with attention being given to the prophylactic use of pyridoxine and the possible need for the use of insulin during tuberculosis treatment.^{27–29}

3.2.1. Treatment of tuberculosis and pregnancy

During pregnancy, the RHZE (R-rifampin,H-isoniazid,Z-pyrazinamide, E- ethambutol)regimen can be administered at the usual doses, and simultaneous use of pyridoxine (50 mg/day) is recommended because of the risk of newborns having spasmodic seizures. Although the medications in the RHZE regimen cross the placental barrier, they do not emerge as teratogens. Regarding breastfeeding, although the medications are present in breast milk in small amounts, there is no risk of toxicity to newborns nor is there any prophylactic effect.^{30–32}

3.2.2. Surgical treatment of tuberculosis

Tuberculosis is treated by using medications, occasionally, it may even be treated surgically in specific cases, especially in cases of drug resistance and in some pulmonary tuberculosis defficult. Surgical lung biopsy has application in the differential diagnosis of pulmonary tuberculosis and lung cancer. The intimaton for surgical treatment include mainly endobronchial tuberculosis, as well as severe adverse reactions, severe hemoptysis, empyema, pneumothorax, and bronchopleural fistula. In tuberculosis residua, surgical interventions may be required in cases of symptomatic pulmonary residue, fungus ball, and hemoptysis.³³

3.3. Drug resistance TB in India

Multi Drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are involving as a major challenge across globe including in India as stated by the World Health Organization (WHO) for success the Stop TB strategy, launched in 2006.MDR-TB: Irregular consumption and frequent interruption in taking treatment for TB is the most common cause of receiving multidrug resistance. In India, MDR-TB amongst new cases is estimated at 2- 3% and amongst re-treatment cases at 14-17%.XDR-TB: XDR-TB has been reported in India, its magnitude remains undetermined as yet due to the lack of laboratories being capable of conducting quality assured second line drug susceptibility testing. TB resistance is now being reported form different parts of world to fighting this growing resistance, in April 2009, WHO recommended member states to take action on multiple fronts towards achieving universal access to

diagnosis and treatment of M/XDR-TB by 2015. In spite of the important progress being made, severe bottlenecks are limiting the responses to the M/XDR-TB epidemic. Indeed, only 10% (24511/ 250000) of the estimated MDR-TB cases among notified TB cases in 2009 in the high MDR-TB countries, and 11% (30475/280000) globally were enrolled on treatment.³⁴ Some countries are making progress by applying policy changes that rationalize the use of hospitals, such as South Africa, or treating patients through community-based models of care, such as the Philippines. However, diagnostic capacity remains limited. moreover, the price of some quality assured second-line drugs has not fallen, and shortages of drugs still occur.

In India where the annual TB incidence rate is approximately 2 million cases per year—the highest of all countries and fourth in the global burden of TB—the extent of MDR-TB incidence is staggering. About 3% of new cases and 12-17% of previously treated cases in India are MDR-TB. Besides this, the WHO ranked India at the bottom among all developing countries in terms of their TB management and control and performance. There is no doubt that the development of multidrug-resistant (MDR)-TB and XDR-TB narrates the apparent weaknesses in primary care services; both diagnostic and treatment services, but it also reflects a failure to country on adhering to the WHO's directly observed treatment, short course (DOTS) strategy. One of the main reasons hypothesized is selective preference of the suspected TB cases to private practitioners. Most TB patients first seek help from one of India's 10 million private practitioners. It is estimated that for most of these patients it is up to 4–6 weeks before they are diagnosed as having TB.³⁵ In addition to this, the TB cure rates for patients who remain with private practitioners are low; it is also estimated that 99,000 MDR-TB cases occur in the country annually. Although the true incidence of both MDR and XDR-TB is impossible to gauge for India, only estimates could be modelled from the reported incidence of known Multi-Drug Resistant Tuberculosis (MDR-TB) cases. To compound the problem further, India has now also been diagnosed with Total Drug Resistant TB.

To address the challenge of MDR-TB, the Revised National Tuberculosis Control Programme (RNTCP) of India has initiated MDR-TB services, at a sub-national level, in 2007 in a limited geographical area and is in the process of expanding these services, in a phased manner, to cover the entire country by 2012. However, due to limited quality assured laboratory capacity in India the program presently enrolls only those patients identified to be at a high risk of MDR-TB (MDR suspects) for diagnostic assessment and subsequent treatment.⁷ RNTCP has limited information on the proportion of MDR-TB suspects amongst TB patients on first line treatment within the program, whether all these MDR-TB suspects are identified and undergo diagnostic assessment and whether all those diagnosed as MDR-

TB are initiated on treatment according to the program guidelines.³⁶

The involvement of civil society organizations and communities in global and national responses to M/XDR-TB remains very limited. Hence, there is an urgent priority to strengthen their active involvement in the response to MDR TB. It is high time to focus advocacy efforts at not only global level but also at country level or state level to ensure that the health sector receives the necessary resources and the M/XDR-TB response remains high on the global health-policy agenda.

With emergence of XDR and TDR in Indian a new debate has also began on the existing DOTS treatment especially for those with drug resistance to continue with the DOTS or initiate Hospital based treatment of resistant cases. However, findings of a systematic review on cost and cost-effectiveness of TB narrates that outpatient-based models of care can greatly enhance the efficiency of treatment for MDR-TB. Considerable amounts could be invested in incentives and enablers (such as food packages and transport vouchers) to minimize the risk of default from outpatient treatment before costs would come close to those for inpatient care. Empirical evidence on the cost-effectiveness of MDR-TB treatment is currently limited to one middle-income country in Latin America, two upper-middle-income countries that were part of the former Soviet Union and one lower middle income country in Asia.³⁷ More country specific data are needed, especially from the two countries that, in combination, account for about 50% of the world's cases of MDR-TB — China and India. Operational research are also suggested to identify the conditions under which outpatient-based models of care specially for migrant populations, HIV TB coinfection and populations with high default rates needs to be considered. Further research on involvement of the different stake holders like private labs, private providers, DOTS providers and convergence with other programs will be required to tackle the menace of MDR TB in India.

4. Conclusion

Tuberculosis diseases caused by mycobacterium tuberculosis as its treatment shown ineffective to many antibiotics due to the evolution of resistant to m.tuberculosis strain which causes multi drug resistance (MDR-TB) and extensively drug resistance (XDR-TB). For reducing the resistant combination therapy of (para-aminosalicylic acid and streptomycin) is introduced for the treatment of pulmonary tuberculosis. XDR-TB mainly includes resistance to isoniazide and rifampicin and MDR-TB includes resistance to fluoroquinolones and one of the SLIDs e.g. kanamycin, amikacin and capreomycin. XDR-TB and MDR-TB are the major challenges across the worldwide for curing and treating the patients. Two different phases in the treatment of TB .1) bactericidal

phase 2) sterilizing phase. In bactericidal phase, killing of highly replicated mycobacterium strain (e.g. Rifampicin, isoniazide, ethambutol, pyrazinamide, streptomycin, PAS, amikacin, kanamycin, cycloserine). Treatment of HIV and tuberculosis also increase the risk of drug resistance and toxicity. For the treatment of tuberculosis and diabetes rifampicin, isoniazide, ethambutol, pyrazinamide are use. Treatment of tuberculosis during pregnancy RHZE drugs can be use they donot show any risk of toxicity or prophylactic effect to newborn. TB can be treated surgically mainly for endobronchial tuberculosis. after XRDTB and MRDTB in india recently total drug resistance has been diagnosed which initiates the DOTS (directly observed treatment strategy) a hospital based treatment.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Gohil CJ, Patel PR, Gohil JJ. Antibiotic drug resistance TB in India. *Int J Pharm Chem Anal* 2021;8(4):145-151.