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Overview of Drug Resistant *Mycobacterium tuberculosis*

Anurag Rai[1]*, Taiyaba khan[2]

[1]Tutor, Department of Microbiology, Prasad Institute of Medical Sciences, Lucknow, India
[2]Tutor, Department of Microbiology, GCRG Institute of Medical Sciences, Lucknow, India

***Address for Correspondence:** Mr. Anurag Rai, Tutor, Department of Microbiology, Prasad Institute of Medical Sciences, Lucknow, India

ABSTRACT

MDR-TB is a global occurrence that poses a serious threat. Tuberculosis (TB) is still the leading cause of death from a single and curable infectious disease. It is the second-most common cause of death from infectious disease (after those due to HIV/AIDS)**.** Its situation is worsened by the presence of multidrug-resistant (MDR) strains of *M. tuberculosis*. In ancient time, it was considered a curse. Tuberculosis started to reemerge in the early 1990s. The completion of the first whole genome sequence of *M. tuberculosis* was in 1998. Multi drug resistant (MDR)-TB is caused by strains of *M. tuberculosis* that resistant to at least rifampicin and isoniazid. Worldwide India is the country with the highest-burden of both TB and MDR-TB. Isolation of MTB on solid media followed by subsequent DST on solid media is easy to perform in the lab. They are time-consuming classical laboratory tests methods. So the molecular method is preferable to detect MTB. Different types of tool are available to detect MDR-TB, XDR-TB. Now-a-days, there are three major commercial alternatives available and they are: GeneXpert, line probe assays (LPA) and Nucleic acid amplification tests (NAAT). The treatment takes too long, many patients are unable to tolerate the combination, and there is a growing threat from multidrug-resistant (MDR) and extremely drug-resistant (XDR)-TB. Reliable and timely detection of drug-resistant TB is needed.

Key-words: Tuberculosis (TB), *Mycobacterium tuberculosis* (MTB), *Mycobacterium tuberculosis* complex (MTBC), Multidrug resistant (MDR), Extensively drug resistant (XDR), Extra pulmonary tuberculosis (EPTB), Nucleic acid amplification tests (NAAT)

INTRODUCTION

M. tuberculosis is the etiologic agent of tuberculosis (TB), a potentially fatal illness which results in approximately 2 million deaths worldwide each year [1]. Tuberculosis is the second-most common cause of death from infectious disease (after those due to HIV/AIDS) [2]. Tuberculosis (TB) is still the leading cause of death from a single and curable infectious disease. In 2012, 8.6 million incident new and relapse cases of active TB disease occurred with an estimated 1.1 million (13%) of incident TB-HIV co-infected patients. The majority of TB cases worldwide were in the South-East Asia (29%), African (27%) and Western Pacific (19%) regions. India and China alone accounted for 26% and 12% of total cases, respectively [3]. According to WHO, in 2016 an estimated 28 lakh cases occurred and 4.5 lakh people died due to TB disease [4].

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MDR-TB is a global occurrence that poses a serious threat to ongoing national TB control programmes. Multidrug-resistant tuberculosis (MDR-TB) is caused by a strain of *M. tuberculosis* that is resistant to at both isoniazid (INH, H) and rifampicin (RMP, R) that are two most powerful 1st line anti TB drugs. According to the 2017 World Health Organization global report, approximately 490000 people were infected by MDR-TB. In addition, there were an estimated 110,000 people who had rifampicin resistant TB (RR-TB). So the number of people estimated to have had MDR-TB or RR-TB in 2016 was 600,000 with approximately 240,000 deaths. [5] Generally TB affects the lungs, but other parts of the body can also be affected [6]. The true sign of active TB is a long term cough with blood-containing sputum, night sweats, and weight loss [7]. There are two types of clinical manifestation of tuberculosis (TB) includes pulmonary TB (PTB) and extra-pulmonary TB (EPTB). EPTB is the TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges). Involvement of Extra pulmonary can occur in isolation or along with a pulmonary focus as in the case of patients with disseminated tuberculosis

(TB). The recent human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) pandemic has resulted in changing epidemiology and has once again brought extra pulmonary tuberculosis (EPTB) into focus [8]. Here, I reviewed some of the insights into the evolutionary history of the tuberculosis disease.

History- Prior to the twentieth century, tuberculosis as a disease was considered to be of little importance to the general population in India [9]. In ancient time, it was considered as curse. TB in India is an ancient disease, and in Indian literature there are passages from around 1500 BCE in which consumption is mentioned, and the disease is attributed to excessive fatigue, worries, hunger, pregnancy and chest wounds [10]. TB started to reemerge in the early 1990s, fuelled by the growing pandemic of HIV/AIDS [11]. According to other dogmas, TB was mainly a consequence of reactivation of latent infections rather than ongoing disease transmission, and that mixed infections and exogenous reinfections with different strains were very unlikely. TB is caused by several species of gram-positive bacteria known as tubercle bacilli or *M. tuberculosis* complex (MTBC). MTBC includes obligate human pathogens such as *M. tuberculosis* and *M. africanum* as well as organisms adapted to various other species of mammal. In the developed world, TB incidence declined steadily during the second half of the 20th century and so funds available for research and control of TB decreased substantially during that time [12]. Robert Koch discovered the causal agent *M. tuberculosis*, and was awarded by Nobel Prize in physiology/medicine in 1905 [13]. Over a long period of time multiple antibiotics required for TB treatment. After the Second World War the first anti-tuberculosis drugs were introduced and then more effective drugs following in early 1950 [14]. The completion of the first whole genome sequence of *M. tuberculosis* was in 1998 [15]. Studies have shown that humans did not, as previously believed, acquire MTBC from animals during the initiation of animal domestication, rather the human and animal-adapted members of MTBC share a common ancestor, which might have infected humans even before the Neolithic transition [16,17].

Drug Resistant Tuberculosis- Tuberculosis (TB) is a serious public health problem worldwide. Its situation is worsened by the presence of multidrug resistant (MDR) strains of *M. tuberculosis*. In recent years, even more serious forms of drug resistance have been reported. Multi drug resistant (MDR)-TB is caused by strains of *M. tuberculosis* that are resistant to at least rifampicin and isoniazid two key drugs in the treatment of the disease. It has been recognized the presence of even more resistant strains of *M. tuberculosis* labeled as extensively drug resistant (XDR)-TB. 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 worrying 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 labeled as totally drug resistant (TDR)-TB.

MDR tuberculosis among household contacts is also reported from several studies. In a study, which was done in northern India and reported 11(2.57%) contacts developed MDR-TB while 4(0.93%) cases developed drug susceptible TB subsequent out of total 428 contacts of the index patient. The Overall rate of disease in the present study was 3.50 % [18].

According to Global tuberculosis control- surveillance, planning, financing in 2008 "Tuberculosis continues to be a leading cause of mortality and morbidity worldwide [19]." According to WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance "The emergence and spread of MDR-TB is threatening to destabilize global tuberculosis control. The prevalence of MDR-TB is increasing throughout the world both among new tuberculosis cases as well as among previously treated ones [20]." WHO reported in 2016 that India has a high burden of MDR-TB and also mentioned that the MDR-TB amongst notified new pulmonary TB patients was 2.8%, whereas amongst notified re-treatment pulmonary TB patients, it was 12% [21]. According to "Global Tuberculosis Control 2016", rates per 100,000 people in different areas of the world are: globally 140, Africa 254, the Americas 27, Eastern Mediterranean 114, Europe 32, Southeast Asia 240, and Western Pacific 95 in 2015. According to the latest World Health Organization (WHO) report, there were an estimated 10.4 million incident cases of TB in 2016 and 1.7 million deaths were attributed to the disease. 250,000 cases occurred in children and 0.4 million deaths were reported among HIV-infected persons.

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The latest Global Tuberculosis Report estimates that 4.1% of new and 19% of previously treated tuberculosis (TB) cases diagnosed in 2015 were multidrug-resistant (MDR). India accounts for one-fourth of the global TB burden. In 2015, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB. India has the highest burden of both TB and MDR TB based on estimates reported in Global TB Report 2016. An estimated 1.3 lakh incident multi-drug resistant TB patients emerge annually in India which includes 79000 MDR-TB Patients estimates among notified pulmonary cases. The incidence of TB is 217 per lakh per year in 2015 and the mortality due to TB is 36 per lac per year in 2015 [5]. Worldwide India is the country with the highest burden of both TB and MDR-TB [5]. There is an estimated 79,000 multi-drug resistant TB patients among the notified cases of pulmonary TB each year.

The current resurgence of TB is mainly due to increasing incidence of resistance of *M. tuberculosis* strains to first-line and important second-line anti-TB drugs and the association of active TB disease with HIV co-infection or other underlying immunosuppressive conditions such as diabetes [22,23]. The WHO has developed the directly observed therapy short course (DOTS) strategy to optimize response and compliance to TB treatment. However, DOTS is labor-intensive and expensive. The global standard first-line regimen is a 6 month course of treatment denoted as 2HRZE/4HR: a 2 months intensive phase of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) followed by a 4 months continuation phase of H and R. The second-line TB treatment, for patients with MDR-TB is based only on observational studies and expert opinion [24]. Clinically, the most advanced regimen [25,26] in this category is known as PaMZ, a combination of the novel nitroimidazo-oxazine PA-824, moxifloxacin and pyrazinamide. [27] The REMoxTB trial [28] replaced either H or E with moxifloxacin (M) in two experimental, 4 months experimental regimens (2HRZM/2HRM and 2MRZE/2MR). This regimen has the potential not only to shorten the duration of first-line treatment, but also to treat a proportion of patients who would previously have needed second-line treatment i.e. patients with MDR-TB [29]. Bacterial burden was reduced more quickly when either bedaquiline (a diarylquinoline formerly known as TMC207) [30] or delamanid (a nitro-dihydro-imidazooxazole formerly known as OPC-67683) [31] was added for 6 months, to an optimized background regimen for MDR-TB [30,31].

Table 1: Genetic basis of drug resistance in *M. tuberculosis* [32-34]

Drug	Gene	Functions
Isoniazid	KatG	Catalase peroxidase
	InhA	Eenoyl-acyl carrier protein reductase
	AhpC	Alkyl hydroperoxidase reductase
	KasA	ketoacyl acyl carrier protein synthetase
Rifampicin	RpoB	β- subunit of the RNA polymerase
Pyrazinamide	PncA	Pyrazinamidase
Streptomycin	RpsL	Ribosomal S12 protein
	Rrs	16S Rrna
Amikacin/kanamycin	Rrs	16S Rrna
Capreomycin	Rrs	16S Rrna
	TlyA	Rrna Methyl transferase
Fluorochinolone	gyrA, gyrB	DNA gyrase
Ethambutol	EmbCAB	Arabinosyl transferase
Ethionamide	GyrB	DNA gyrase
	InhA	Enoyl-acyl carrier protein reductase

The WHO Guidelines for the management of drug-resistant TB have categorized available anti-TB drugs into five groups, based on known efficacy.

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Table 2: Alternative method of grouping anti-tuberculosis drugs [35]

Grouping	Drugs
Group 1	Isoniazid (H), Rifampicin (R)
First-line oral agents	Ethambutol (E), Pyrazinamide (Z)
Group 2	Kanamycin (Km), Amikacin (Am)
Injectable agents	Capreomycin (Cm), Viomycin (Vm)
	Streptomycin (S)
Group 3	Moxifloxacin (Mfx), Levofloxacin (Lfx)
Fluoroquinolones	Ofloxacin (Ofx)
Group 4	Ethionamide (Eto), Protionamide (Pto)
Oral bacteriostatic second-line	Cycloserine (Cs), Terizidone (Trd)
Agents	*p*-aminosalicylic acid (PAS)
	Clofazimine (Cfz), linezolid (Lzd)
Group 5	Amoxicillin/clavulanate (Amx/Clv)
Agents with unclear role in MDR-TB	Thioacetazone (Thz), Imipenem/cilastatin (Ipm/Cln)
treatment (not recommended by WHO)	High-dose isoniazid (high dose H), Clarithromycin (Clr)

Lab Diagnostic Tests- According to now-a-days known epidemiological situation and diagnostic tools, it cannot be considered acceptable to wait for 8–10 weeks to know if a clinical isolate is drug susceptible or not. Thus, the generally used algorithm of isolation on solid media followed by subsequent DST on solid media must today be seen as obsolete. Different types of tool are available to detect MDR-TB. They are time-consuming classical laboratory tests methods and molecular techniques. According to Sven Hoffner [36] the most rapid and promising techniques are based on molecular detection of resistance-related mutations, especially when the assay is used for direct testing of a smear-positive sputum sample. In this case MDR-TB patients can be detected in 1–2 days which makes early initiation of effective drug combinations possible. Now-a-days, there are three major commercial alternatives: GeneXpert, line probe assays (LPA) and the Nucleic acid amplification tests (NAAT). The Xpert system is the most rapid technique, and it was developed to be easy to use. It offers the simultaneous detection of M. tuberculosis and resistance to rifampicin, which is seen as a proxy for MDR-TB. Rifampicin is, however, not everywhere an applicable MDR marker. For example, in Iran, the prevalence of rifampicin mono-resistant *M. tuberculosis* is high.

The LPA investigated resistance to both rifampicin and isoniazid and is thus more informative. It is, however, somewhat more time-consuming and laborious to perform. Both assays have demonstrated excellent specificity and sensitivity. Where phenotypic DST assays are shown to be more sensitive to detect a small proportion of drug-resistant bacteria [36].

The development of molecular techniques to differentiate between strains of MTBC made it possible to readdress some of these points. One of these methods, a DNA fingerprinting protocol based on the Mycobacterium insertion sequence IS6110, quickly evolved into the first international gold standard for genotyping of MTBC [37]. It also became a key component of pragmatic public health efforts, such as detecting disease outbreaks and ongoing TB transmission [38] and allowed differentiation between patients who relapsed due to treatment and those reinfected with a different strain [39]. Biopsy and/or surgery are required to procure tissue samples for diagnosis and managing the complications. Further research is required for evolving the most suitable treatment for EPTB [8].

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CONCLUSIONS

The treatment takes too long, many patients are unable to tolerate the combination, and there is a growing threat from multidrug-resistant (MDR) and extremely drug-resistant (XDR)-TB. Reliable and timely detection of drug-resistant TB is needed. In MDR, timely detection of the XDR defining agents and PZA is urgently needed. Early detection of all forms of drug resistance in TB is a key factor to reduce and contain the spread of these resistant strains. A better knowledge of the mechanisms of action of anti-TB drugs and the development of drug resistance will allow identifying new drug targets and better ways to detect drug resistance. The important approach to TB drug development that can yield results rapidly is to repurpose drugs that also have activity against TB.

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