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Multidrug resistant and Extensively drug resistant TB: A Nuisance to Medical Science

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Abstract

Tuberculosis is the topic of discussion for researchers due to the indocile nature of its causative micro-organism, *Mycobacterium tuberculosis* H_{37}Rv (MTB). MTB escapes the human immune system by employing different strategies to render the drugs used for treatment ineffective, due to ultimate alterations in genes such as gyr 90, 91 and 94 which make it resistant to different drugs. Different techniques and methodologies are being developed and used to diagnose, treat and prevent the spread of the disease caused due to drug-resistant MTB. Drug resistance is reported from all over the world. Although very less treatment options are available in case of MDR and XDR-TB but still they are curable. HIV co-infection is also a big hurdle in the way of successful treatment of drug resistant TB as drug-drug interaction is an issue. It is better to improve the community medicine system to battle the TB in a better way. Highest percent of people is showing the resistant against INH so one should be careful about this fact while using the INH in regimen.

Keywords: Mycobacterium; Tuberculosis; MDR-TB; XDR-TB; Virulence factor

Abbreviations: TB: Tuberculosis, MDR-TB: Multi-Drug Resistant Tuberculosis; XDR-TB: Extensively Drug-Resistant tuberculosis; TRC: Tuberculosis Research Centre (Chennai); CTD: The Central TB Division; DRS- Drug-Resistance Surveillance; RNTCP-NTI: National Tuberculosis Institute; IUATLD: International Union Against Tuberculosis and Lung Disease; INH: Isoniazid; RIF: Rifampicin; INH-RIF: Isoniazid-Rifampicin; RNTCP: Revised National TB Program; WHO: World Health Organization; DOTS-Directly Observed Treatment Short Term Course; GYR: Gyrase; KAT G: Catalase Peroxidase Enzyme; PAS acid: Para-Aminosalicylic acid

Introduction

Tuberculosis is a disaster to the medical science due to the multi-faceted dimensions of the survival strategies employed by *Mycobacterium tuberculosis* H_{37}Rv (MTB) to escape the immune system of the host. Moreover, due to improper treatment and management, tuberculosis has emerged to be more powerful in the form of two deadly infectious diseases, namely Multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). When MTB strains become resistant to the first line drugs; isoniazid and rifampicin, with or without resistance to the anti-TB drugs it is termed as MDR-TB. And, when it becomes resistant to any of the flouroquinolones and any of the second line injectable drugs in addition to MDR-TB then it is termed as XDR-TB [1].

The emergence of MDR-TB was first noticed in 1990s. WHO and International Union against TB and Lung Disease conducted three rounds of surveys between 1996 and 2002. As per the estimates of surveys, the prevalence of MDR-TB was 0% in eight countries to 14.2% in Kazakhstan and Israel. Among the new cases with the median prevalence of 1.1% and the median prevalence among the previously treated cases was found to be 7% [2]. But latest figures are more horrible and showing the median prevalence of 1.6% among the new cases and 11.7% among previously treated cases [3]. According to surveys from 184 countries, 458000 new MDR-TB cases occurred worldwide in 2003 and out of these cases, 60 % cases were reported from China and India constituting 3.2% of all new TB cases [2], which is also expected because these two countries are two most populated countries of the world and a major part of their population cannot afford expensive treatment. Drug resistance scenario of India (Figure 1) is horrible and they are due to its huge population, higher population density, lack of a good public health care system and poverty, and this data is based on studies conducted in different regions of India at different time points between 1980 and 1999. Although this is old data but it is signifying the threat of this deadly disease in this part of world. A comparatively latest study from Kashmir valley (India) is showing the highest prevalence of MDR-TB among the new cases, in any part of India, till date [5]. Latest data from China (Figure 2) and Europe (Figure 3) is also telling the same story.

The term XDR-TB was first publicly used by Centers for Disease

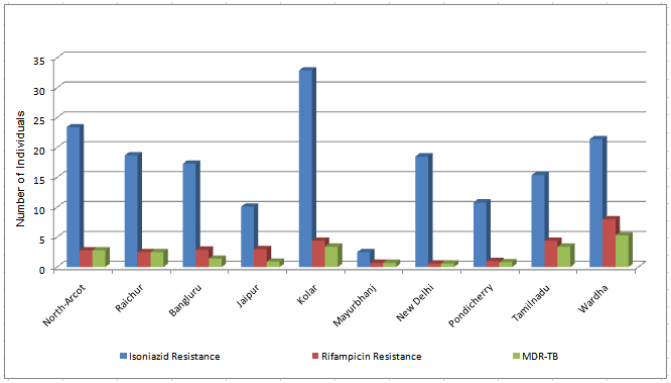

Figure 1: Drug Resistance scenario of different parts of India [4].

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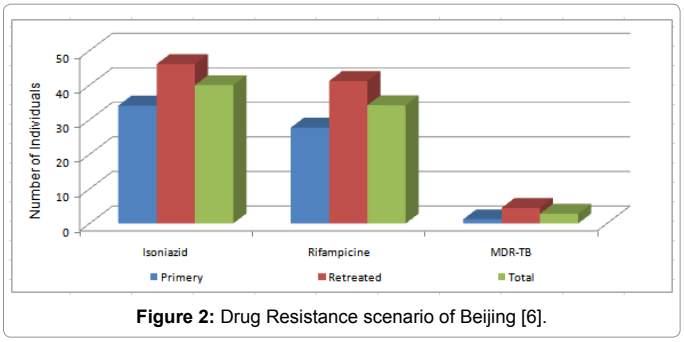

Figure 2: Drug Resistance scenario of Beijing [6].

Control and Prevention (CDC) at the 36th World Conference on Lung Health in Paris, France in March 2005 [8, 9] but original definition of XDR-TB was first published in literature in March 2006 [10]. Outbreak of XDR-TB came into limelight in September, 2006 for the first time; in a rural hospital in Tugela Ferry in South Africa. 53 cases of XDR-TB were diagnosed, out of which 52 patients died [11]. Comparative recent data from 18 countries of Europe is showing 10% prevalence of XDR-TB among the MDR-TB cases for which DST results for SLD was available [12]. Study conducted at All India Institute of Medical Sciences, New Delhi, India, is showing the prevalence of XDR-TB is 2.4% among the MDR-TB cases [13], but these figures are not giving the right picture of XDR-TB scenario in India because sample size is small and all cases belongs to only one hospital. The actual dimensions of prevalence of XDR-TB are still not defined due to the lack of infrastructure and well equipped laboratories to diagnose it in many countries.

Potential causes of MDR-TB and XDR-TB

Factors related to treatment history: In most of the countries which are adversely affected by drug resistant TB, public health care system is not very good and private practitioners are not used to maintain the treatment history of patient and due to this patient are subjected to be treated improperly.

Improper and incomplete treatment: Mismanagement of the treatment for instance, prescribing a single drug and later on adding up off another drug to the collapsing regimen, undiagnosed pre-existing resistance to drugs, prescribing inadequate regimen, inadequate follow up of the regimen by the patient results in the reduced susceptibility of the patient to anti-TB drugs. Non –adherence to the prescribed regimen is mostly ignored by the clinicians dealing with the treatment which makes the patient susceptible to MDR-TB and XDR-TB [2, 14, 15]. The patients are reluctant to adhere to the prescribed regimen due to the adverse effects of the most of the anti-TB drugs (Table 1) [2]. Incomplete treatment and improper regimen, both poses a selection pressure on the drug resistant strains that's why the prevalence of MDR-TB is higher among the retreated patients compared to the new cases (Figure 4, 5).

Infrastructure: Due to the lack of well equipped laboratories and facilities for growing culture for determining the sensitivity of the *Mycobacterium* to the applied drugs in developing nations, the diagnosis is often made inferring the treatment history of the patient (which is also not very well maintained in most of the cases) and logarithms [2].

Mutation: Mutations at the different sites in the different genes in MTB are actually responsible for the resistance caused for the drugs. Every drug has a unique target in MTB and when there are perturbations in these target sites the drug is rendered inefficient for that specific purpose for which it has been designed. Genes responsible for drug resistance in MTB after mutations are listed in (Table 2).

Multi-drug transporter proteins: Multidrug transporter proteins mediate both acquired and intrinsic resistance to anti-TB drugs. The human analogue for this protein is P-glycoproteins, which is expressed on the effector cells of immune system and has been shown to be over expressed in the experimental cell lines on the infection of MTB hence the accumulation of isoniazid inside the cells is reduced [17].

Diagnosis

Till now we don't know the very clear picture of drug resistance from many part of the world [1] and diagnosis is the key factor in the spreading of drug resistant TB. So in order to control the spread of drug resistant TB, diagnosis should be accurate and on time and to accomplish this purpose diagnostic centre and other health care services should be easily accessible by the patients. The diagnosis can be done by conventional methods like, a) absolute concentration method, b) the resistance ratio method and c) proportion method using Lowenstein Jensen culture for testing drug sensitivity or by newer methods like radiometric methods, e.g., Benton-Dickinson method Franklin lakes, BACTEC-460 etc. Also, the methods like mycobacteria indicator tube (MGIT) system, restriction fragment length polymorphism (RFLP) patterns to categorize different isolates of MTB for better understanding of molecular epidemiology of TB, use of ligase chain reaction (LCR), luciferase reporter assay, FASTPlaque TB-RIL, a rapid bacteriophage based test, polymerase chain reaction (PCR), the Line Probe Assay (LiPA) are also being used for better analysis of MDR-TB and XDR-TB [2, 17].

Treatment

XDR-TB has higher mortality rate than MDR-TB as it has fewer options available for effective treatment than MDR-TB. Previously it was thought that XDR-TB is untreatable, but now it has been proved that it can be cured using appropriate treatment regimen. Although the success rate is not very good but studies have shown that XDR-TB patients co-infected with HIV can also cured [18].

Designing drugs for MDR-TB and XDR-TB is extremely difficult as in the beginning the tubercle bacilli may remain in dormant state for a long time and grow slowly. Moreover, the perturbations in the genes may make it unsusceptible to many drugs which may be able to penetrate the cell wall, disrupt the eradication mechanism in macrophages and lie there creating a second permeability barrier [19].

The principles for the treatment of both MDR-TB and XDR-TB are same. Extensive chemotherapy is carried out for about 2 years [20]. The anti-TB drugs should be consumed according to the prescribed daily dosage by WHO (Table 3) to prevent drug resistance in MTB.

The old drugs like clofazimine and its analogues, aminoglycosides, quinolones, the macrolides and rifubutin may also be prescribed in better regimens. Drug-repositioning of old anti-TB drugs may also help in developing better therapies as it does not require additional funds for bringing the drug to the market as they are already being marketed, for e.g., clofazimine, rifabutin, macrolide antibiotics, beta-lactamase inhibitors and aminoglycosides [22].

Genetic engineering may also play a vital role in the eradication of MDR-TB and XDR-TB as the genome of MTB has been sequenced. The metabolic pathways are known and can be attacked by suitable designed drugs. The transcription in MTB can be interrupted by the destruction of the transcription factors that bind DNA. Anti-sense nucleic acids can be delivered with the help of phages which inhibit the expression of MTB genes. Alterations in the genetic products of MTB may be utilized to cause self death of MTB [22]. Some new methods for

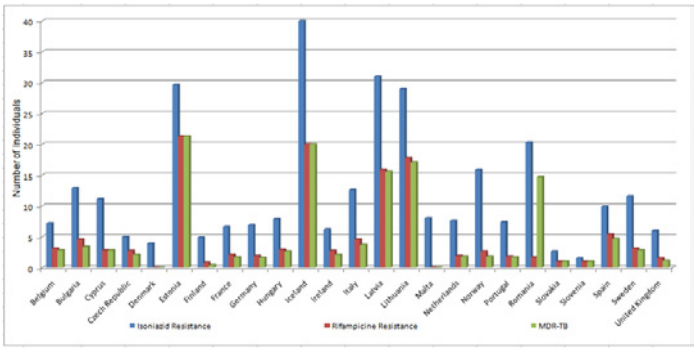

Figure 3: Drug resistance scenario of different countries of Europe [7].

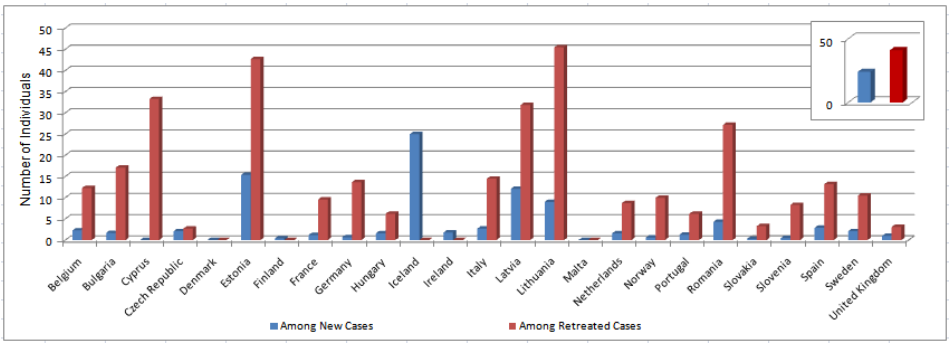

Figure 4: Showing the higher drug resistance in retreated cases than new cases, in Europe [7] and Mumbai (in inset) [16].

Drug	Adverse drug effect
Amikacin, kanamycin streptomycin	Ototoxicity, nephrotoxicity, agranulocytosis, lupoid reactions, aplastic anaemia, thrombocytopenia and hemolytic anemia
Ethambutol	peripheral neuritis, dose-dependent optic neuritis
Terizodone	headache, insomia, tremors, depression,suicide risk, confusion and risk of psychosis.
Cycloserine	convulsions and slurred speech
Flouroquinolones	Gastrointestinal perturbations, dizziness, altered mood, headache and sometimes convulsions.
Capreomycin	Enhances the effect of neuromuscular blocking agents, administered in anesthesia, cutaneous reactions, hepatotoxicity, hypocalcemia and hypokalemia.
Aminoglycosides	Cause pain at the injection site
Thioamides, ethioamides and prothioamides	Leads to sulphurous belching, metallic taste, nausea, anorexia, epigastric discomfort, vomiting and excessive salivation, psychotic reactions including hallucinations and depression, hypoglycemia, hypothyroidism, gynacomastia

Table 1: Adverse effects of some anti tuberculosis drugs [2].

Drug	Genes Responsible For Resistance
Streptomycin	Ribosomal S12 protein (rpsl), 16S rRNA (rrs), Aminoglycoside phosphotransferase gene (strA)
Isoniazid	Catalase-peroxidase enzyme (kat G), Alkyl hydroperoxidase reductase (ahpC), Oxidative stress regulator (oxy R)
Rifampicin	RNA polymerase (rpoB)
Isoniazid-ethionamide	Mycolic acid synthesis (inhA)
Ethambutol	Arabinosyl transferase (emb A,B,C)
Flouroquinolones	DNA gyrase (gyr A&B)

Table 2: Anti-TB drugs and genes responsible for their resistance [2].

	Drug	Daily Dosage		Tolerance	Toxicity
		Min.	Max.		
	Aminoglycosides				
1.	Streptomycin	750	1000	Moderate	Medium
	Amikacin	750	1000	-	-
	Kanamycin	750	1000	Poor	Medium
	Capreomycin	750	1000	Moderate	Medium
	Thioamides				
2.	Ethioamide	500	750	Moderate	Moderate
	Prothioamide	500	750	Moderate	Moderate
3.	**Pyrazinamide**	1200	1600	Moderate	Low
	Flouroquinolones				
4.	Ciprofloxacin	1000	1500	Good	Low
	Ofloxacin	600	800	Good	Low
5.	**Cycloserine**	500	750	Moderate	High
6.	**Ethambutol**	1000	1200	Good	Low
7.	**PAS Acid**	10g	12g	Poor	Low

Table 3: Anti- TB drugs and their daily dosage [21].

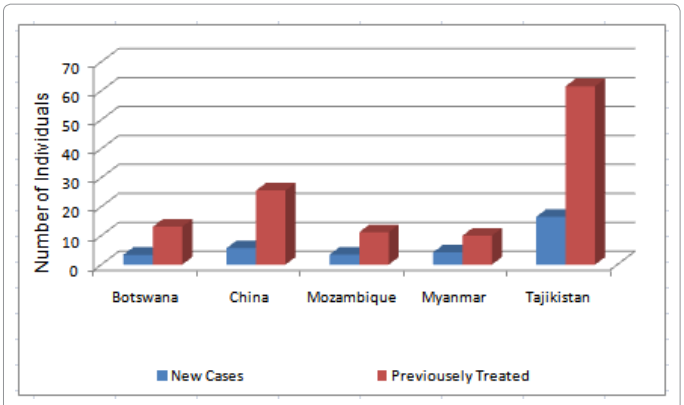

Figure 5: Showing the higher drug resistance in retreated cases than new cases in different countries, reported by WHO [1].

delivering drugs may also be helpful in the treatment of MDR-TB and XDR-TB, like use of liposomes.

MDR- TB and XDR-TB with HIV

Being immuno-compromised, the HIV/AIDS patients are at a greater risk than normal person [15, 23, 24-25]. But fortunately reports have shown that HIV status of patient is not strongly associated with drug resistant TB [26]. It means despite having a weakened immune system, patient have drug-susceptibility, and can be treated with standard first line anti-TB drugs. TB can be treated using six month standard regimen and in case of HIV, this may be up to two years in case dependant manner and for HIV we have a lifetime regimen mainly dependent on antiretroviral therapy. In HIV infected TB patients this is a very big question that what should be the treatment regimen. Either provide the treatment first for tuberculosis and then for HIV infection or give both the treatments at the same time. Studies have shown that outcomes of dual AIDS-TB treatment therapy are better than delayed antiretroviral therapy [27]. But some big challenges are also associated with the dual AIDS-TB treatment regimen i.e. drug–drug interaction, drug–disease interactions, immune reconstitution inflammatory syndrome (IRIS), shared drug toxicities, and high pill burdens [28].

The treatment of MDR-TB and XDR-TB patients who are HIV positive is a great challenge to the medical science because the drug-drug interaction in HIV patients who consume high number of drugs consisting of both anti-TB drugs and anti-retroviral drugs, it is difficult to monitor the success of the prescribed regimen. However, in HIV positive people, when treated with antiretroviral regimen, showed better outcomes for XDR-TB and MDR-TB treatment comparison to HIV positive people, who did not treated with antiretroviral regimen [3].

Public health responsibilities of health care providers [29]

- All the MDR-TB and XDR-TB cases should be immediately reported to the respective District Officer by the Health Care Centers and clinicians dealing with the treatment and must intimate regarding the regimen and its outcome.
- The family members of MDR-TB and XDR-TB patients should be counseled regularly right from the initiation of the treatment till the end of it.
- All the family members and other contacts of the person under treatment should be screened, so as to detect any other case of active TB acquired from the patient.
- All the practitioners and health care centers must develop a program to check the nosocomial transmission of TB and also must see that it is effectively implemented.
- Any interaction of the practitioners and health care centers should be done wisely and carefully so as to avoid the development of any myth related to MDR-TB and XDR-TB and to avoid any panic caused to the people due to the deadly infectious nature of the strains causing these diseases.

Need of the hour

The urge of the present scenario of MDR-TB and XDR-TB is to develop reliable and rapid detection method of MDR and XDR strains of MTB. By developing the markers for detection of MDR and XDR strains of MTB we will be able to detect MDR and XDR-TB at right time, Luo et al. have done such a work that may become very helpful around the world for the detection of MDR and XDR-TB [30]. There is also a requirement of in depth studies of co-infected patients of TB and HIV and their treatment outcomes.

As the older drugs are becoming ineffective on MTB which is a big threat for human being. So we should always look for newer drug targets then only we will be able to cure MDR and XDR-TB. People are working very well in this direction and recently some newer potent drug targets have been reported and MEP pathway of MTB is one of them [31]. DNA gyrase of MTB can also be exploited as drug target for the treatment of drug resistant TB [32]. We can also think of to modulate the host immune system to combat with this bug in an efficient way but it is always difficult to do something with human than a bacteria.

Moreover, people are trying to find out the treatment for drug resistant TB on the basis of Indian traditional knowledge of medicinal plants and people have identified such medicinal plants which show significant activity against drug resistant strains of MTB [33].

Conclusion

Drug resistant TB is imposing a threat of survival for human beings and till date we are not having any effective treatment against these two deadly forms of tuberculosis named as MDR and XDR-TB. Whatever treatment we are having, against these two form of disease, that is having a lot of side effects also. More percentage of people are resistant against INH (Figure 1, Figure 2 and Figure 3) and literature tells that this is the highest percent resistant against any anti tuberculosis drug. So this is clear that MTB strains are more prone to get resistant against INH. So physician should regularly check for the INH resistant and should plan the regimen accordingly.

Diagnosis and treatment of drug resistant TB is not accessible to a large fraction of world's population and very expensive also. Inaccessibility, expensiveness of treatment & diagnosis and the side effects caused by anti TB drugs is the major hurdle in the way of eradication of TB from the world.

Previously it was thought that the TB is a disease of poor (like India, China and African country) but a recent data on XDR from Europe is showing that this disease doesn't differentiate between rich and poor [12], data from the USA is also telling the same story [34]. We all know that TB is an infectious disease spread by air so although, we are taking care of disease at individual level but we should study and understand the drug resistant TB at communitywide level and such studies have been conducted by Murase et al. and future such studies may help us to treat this disease at communitywide level [35]. Till now our knowledge

is very limited in the cases of co-infection of TB and AIDS. So, more studies should be conducted in this area for better treatment of such patients.

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