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A Brief Review of Current Status of Drug- Resistant Tuberculosis with Special Reference to India

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Abstract

Tuberculosis (TB) remains one amongst the most chronic communicable diseases being a serious community health problem in the world. Pathogenic bacteria Mycobacterium tuberculosis causes this disease, which generally have an effect on the lungs but may also adversely affect other organs. M. tuberculosis can build up resistance against the antimicrobial therapeutic drugs which are frequently used to cure the disease. There exist different types of tuberculosis (DR-TB) which are resistant to the drugs prescribed for its treatment. Some selective strains of the TB bacteria develop resistance to the standard drugs through the mechanism that involves genetic alteration. Improper treatment of the disease and its horizontal transmission in the community remain the major reasons of increase in the frequency of drug resistant TB. In India, an estimated burden of this disease remains 2.69 million cases. Higher mortality rates have been reported in TB-HIV co-infection cases. This review portrays the current status of this chronic disease with special reference to India.

Keywords: Drug- Resistant, Tuberculosis, India

Introduction

Tuberculosis (TB) is a serious community health problem in India and other developing countries of the world. Globally, tuberculosis (TB) remains one of the highly prevalent chronic communicable diseases which is caused by *Mycobacterium tuberculosis* which generally affects the lungs with warning signs of cough, shortness of breath, chest pain and fever, but may adversely affect other organs as well showing distinct symptoms (Kochi, 1991; Zaman, 2010). Tuberculosis (TB) bacteria are spread mainly through the air in the community. The bacteria are released in the aerial environment by someone who already has the TB infection through tiny droplets via coughs and sneezes. Many factors involving poor environmental conditions, climate change, globalization, urbanization, and population growth contribute to emergence of Tuberculosis (TB) in human populations (Lindahl and Grace, 2015).

Firmly followed six month drug regimen cures majority of patients with TB under appropriate treatment strategy whereas, inappropriate administration of antimicrobial drugs or incorrect formulations of therapeutic drugs and premature treatment walk out lead to drug resistance (WHO, 2018). Immune system usually can prevent someone from becoming sick even if there is infection of tuberculosis bacteria hence; there remains distinction between the latent and active conditions of TB. In latent TB, symptoms are not apparent due to inactive state of the bacteria however; these can turn into active TB condition. In active TB, infected person remains sick and in most cases can spread this to others. One can show symptoms of active TB in the first few weeks after infection with the TB bacteria, or it might occur years later. Many strains of tuberculosis resist the drugs which are used to treat the disease and this condition is known as drug resistant tuberculosis (DR-TB).

Drug Resistant Tuberculosis (DR-TB)

There exist different categories of Drug resistant tuberculosis (DR-TB). Mechanism of spread of Drug-resistant TB (DR-TB) is similar to drug-susceptible TB (Goyal *et al.* 2017; Lakhani *et al.* 2019). Of note, in

some literature, all the forms of RR-TB including MDR-TB, are termed as 'RR-TB'. Moreover, while a specific form of RR-TB is cited, it is referred to in more characteristic feature e.g. rifampicin mono-resistant TB; fluoroquinolone-resistant RR-TB.

i). Rifampicin-resistant TB (RR-TB)

This refers to *Mycobacterium tuberculosis* strains that are at least resistant to rifampicin that may or may not involve resistance to other potent drugs. This group involves rifampicin mono-resistant TB, MDR-TB, pre-XDR-TB and XDR-TB drugs (Prasad, et al. 2008). Treatment of this condition remains difficult and complicated hence requires experience and skills. Emergence of this condition can be prevented by prompt diagnosis and effective treatment.

ii). Multidrug-Resistant TB (MDR TB)

The strains that cause Multidrug-resistant TB (MDR-TB) show resistance against in any case the two most potent TB drugs rifampin and isoniazid. These drugs are important therapeutic agents used in the treatment regime of wide spectrum of TB disease. As cited by Prasad, et al. (2008), the incidence of MDR-TB was noted to be very high at 40% in some states of India during 2006 and 2015. Nearly, 36% of all patients who were given treatment earlier developed MDR-TB.

iii). Extensively drug resistant (XDR-TB)

Extensively rare condition of the TB disease known as extensively drug resistant TB (XDR-TB) is caused by the strain which shows resistance against rifampin and isoniazid, in addition to any antibiotics belonging to fluoroquinolone group of drugs and in any case one of three second-line drugs which involve amikacin, kanamycin, or capreomycin. In persons with weak immune system due to HIV or other conditions XDR-TB poses special concern because of its effective resistance against the strongest TB drugs. Hence, patients have much less effective treatment options. They remain more vulnerable to develop TB once they encounter infection being at higher mortality risk. This clinical condition has been found incidental in 117 countries worldwide (WHO, 2018).

iv). Super-XDR-TB (TDR-TB or XXDR-TB)

This refers to the strains that show drug resistance against all of the first and second line drugs. In India, multidrug tuberculosis shows an alarming trend and is slowly turning into a significant public health problem (Lakhani *et al.* 2019). In 2009, the TDR-TB was reported for the first time from neighboring country Iran where the patients suffering from TB showed resistance against all the potent first line (FLDs) and second line (SLDs) anti-tubercular drugs. Earlier, it was in 2007 in Italy, when the term 'extremely drug resistance tuberculosis (XXDR-TB)' was coined for the subjects noncompliant to all FLDs and SLDs. Later in India, patients of TDR-TB were reported for the first time in 2012 (Chaturvedi et al. 2012).

Incidence

Globally, tuberculosis (TB) affects more than 8 million people and cause nearly 1.7 million TB-related deaths annually. This figure involved females, children and predominantly males in all countries and age groups. This disease mostly affects adults yet, all age groups remain at risk. Developing countries have shown more than 90% of cases and overall deaths (Goswami and LoBue, 2020; WHO, 2018).

In India, TB statistics is provided since 1997 by the Revised National Tuberculosis Control Programme (RNTCP). Estimated burden of this disease remains 2.69 million cases (WHO, 2018). The greater part of population has latent TB rather than TB disease (Kiazyk and Ball, 2017) hence; it is assessed that a great proportion of Indian population gets TB infection. Nearly 2 million people in the world with multi drug or

rifampicin-resistant TB (MDR/RR-TB) were reported in 2019 (WHO, 2020). India had nearly 27 thousand MDR-TB cases being the highest in the world. Beside this, XDR-TB cases were nearly 2 thousand in India (WHO, 2018).

In people living with HIV (PLHIV), tuberculosis (TB) remains the foremost reason of morbidity and mortality. Persons with PLHIV are 20 times more vulnerable to TB infection as compared to persons without HIV. Higher mortality rates have been reported in TB-HIV co-infection cases. Nearly one fourth deaths of PLHIV are observed to be linked with TB (WHO, 2020).

Susceptibility to TB

There are several environmental factors that contribute to TB infection in human. These factors involve physical condition, life style (smoking etc.), socio-economic factors and Poor environmental conditions. Apart from this, genetics plays a vital role in susceptibility to Tuberculosis. Significant association of prevalence of Tuberculosis with specific ethnic groups, geographical regions and cultures support role of genetic factors in susceptibility to Tuberculosis in human populations. The mechanism of this involves genetics of both host and pathogen (Hu et al. 2015). Moreover, understanding of *M. tuberculosis*-host interaction remains equally imperative for learning the mechanism of invasion of bacteria in host defenses and development of disease.

Recently Li Cai et al. (2019) reviewed the connection of various candidate genes with TB, involving the human leukocyte antigen (HLA) gene, the solute carrier family 11 member 1 (SLC11A1) gene system, the mannan-binding lectin (MBL) gene, the vitamin D receptor (VDR) gene, the P2X7 receptor (P2X7) gene and the speckled 110 (SP110) gene. It is emphasized that the discovery of these candidate genes can be helpful in revealing the pathogenic mechanism and strength of TB. This can provide scientific evidence and pave the way for formulating the related measures of prevention and remedies.

Causes of Drug Resistant Tuberculosis (DR-TB)

Drug Resistant tuberculosis is believed to be artificial adversity due to carelessness of patients and medical practitioner. Inadequate dose of medicines, its duration and disobedience to the prescriptions result in the development of this disease. Additional causes involve inadequate use of sputum smear microscopy and immense trust on chest radiography (Chaturvedi et al. 2012). Besides, increased complexity in treating the Drug Resistant Tuberculosis (DR-TB), the patient remains infectious for long hence; increasing the threat of infection to other persons (CCOSH, 2020; Dheda *et al.* 2017).

Mechanism of Drug Resistance

There are certain mechanisms involved that confer resistance against remedial drugs provided for treatment of tuberculosis (Sandhu and Akhter, 2017). Certain variants of the TB bacteria develop resistance to the potent drugs through genetic variations. Beside this, the complex lipid molecules of the cell wall of *M. tuberculosis* (TB) function as an obstacle to stop drugs from entering the cell (Knechel, 2009; Mitchison, 2004). Another way is through bacterial genome that codes for enzymes or proteins which cause inactivation of molecules of therapeutic drugs. It is also hypothesized that there might exist some molecular systems that actively pump drug molecules out of the cell. Moreover, spontaneous mutations in the bacterial genome alter those proteins which are the target of therapeutic drugs, creating the bacteria drug resistant (Louw et al. 2009).

Detection of Drug resistance

Molecular (such as Xpert MTB/RIF) and/or culture-based laboratory tests are carried out to detect drug resistance by testing bacteria for sensitivity to the specific drug(s) or investigate resistance patterns. Molecular approach of testing gives results in short time and has many benefits over culture-based tests. Moreover, low resource setting is required for molecular approach of testing (Gupta and Anupurba, 2015; WHO, 2018).

Genetic mutations in the DNA of TB bacterium causes drug resistance in TB. These mutations are clustered together in specific segments or genes in the DNA for some anti-TB drugs, while for others the mutations are spread throughout the DNA or genome of the bacterium. These genetic mutations can be detected by DNA sequencing method in order to identify specific genetic alterations that confer drug resistance against specific anti-TB drugs involving rifampicin, isoniazid, fluoroquinolones and injectables (Ahmad and Mokaddas, 2009; WHO, 2018).

Prospective Therapeutic Opportunities

The current drugs or drug combinations used to treat millions of TB patients are based on discoveries and clinical experiences yet, these course of therapies remain limited by the long duration, emergence of resistance power of bacteria and permanent tissue damage of the host. In last few years we have learned much new information in context of physiology of TB infection whereas, only one drug was discovered in last three decades. Despite this, efforts are on to develop new therapeutic drugs for wide spectrum of bacterial strains (Baer et al. (2015; Mdluli et al. 2015).

Baer et al. (2015) discussed recent biological research outcomes for the consistent development of more successful therapeutics. They discussed emerging approaches into bacterial physiology suggesting new pathways that might be utilized to hasten therapy. Moreover, genetic synergy concept can be useful in designing effective combination therapies. Apart from these two tactics, promising approaches to amend the host response to intensify antibiotic efficacy were suggested. They claim that these tactics would bring about more effective drug development for remedy of TB.

Management of MDR-TB in India

In India, treatment centers have been expanded with introduction of newer drugs, shortened duration of treatment and strengthening of drug safety monitoring in order to manage MDR-TB. Moreover, treatment initiation has been made more patient friendly. Shorter regimen for MDRTB has been introduced in all the states. Regimens with Bedaquiline and Delamanid, have been made available with nearly 3 thousand patients enrolled and Delamanid use in children belonging to 6 to 17 years has also been initiated. In the country, aligned with ambitious National Strategic Plan, there appeared effective policies and interventions in last few years for ending this chronic disease (India TB Report, 2019). In years to come, there will be focus towards streamlining, strengthening and intensifying the strategic plan and services to end TB in India.

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