Drug-resistant Tuberculosis: A Global Health Concern

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Abstract

Drug-resistant tuberculosis is a re-emerging public health concern which requires special attention all around the world. Among all the infectious diseases, drug-resistant tuberculosis is now the most lethal infection causing disease in both children and adults. The co-infection of HIV with tuberculosis increases the mortality rates globally. The resistance follows two mechanics: either it will be intrinsic or acquired; both are equally drastic for the health of the individuals. The phenotypic methods for the detection of drug-resistant tuberculosis include culture methods. In culture methods bacteria are introduced in a medium with anti-TB agents to check if it is resistant or susceptible to particular anti-TB agents. In genotypic methods, advanced tools are used for the purpose of diagnosis for bacteria such as LPAs. The treatment of TB involves drug therapy for at least four months or more while specific drugs are given to the patients. First-line and second-line TB drugs are more commonly used for the treatment purposes. The chapter explains the mechanism of resistance, diagnosis and treatment regimens used for drug-resistant tuberculosis.

Keywords: *Mycobacterium tuberculosis,* Antimicrobial resistance, Drug-resistant tuberculosis, Latent TB, Active TB, Intrinsic resistance, Acquired resistance,and Treatment regimens

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Introduction

One of the most important public health issues worldwide is the antimicrobial resistance which also now possess health security concerns globally (WHO, 2009; Uplekar et al., 2015). While focusing on the bacterial infections which are resistant to many related drugs, drug-resistant tuberculosis gains much importance, specifically its diagnosis and therapeutic measures (Koch et al., 2018). Among several epidemics which affect the health of individuals on global levels, tuberculosis is considered the most important of all of them. The lethal infection of tuberculosis is caused by the bacteria called *Mycobacterium tuberculosis* (Figure 1). Since the old times, tuberculosis (TB) has been known for its high morbidity and mortality rates making it a deadly threat for public health (Ghodbane & Drancourt, 2013; Shuaib et al., 2022). According to the research data, tuberculosis exceeded all the infectious diseases including HIV/AIDS, having the highest death rate all around the world. The main causes of drug-resistance among different strains of *M. tuberculosis* are genetic characteristics of the host, virulence of the bacteria, co-infection of HIV, and incomplete treatment of the infected individuals. All these factors contribute to the development of drug resistant TB (Khawbung et al., 2021). The outbreak of resistance among different variants of TB makes the treatment of the TB even more challenging. Individuals who do not follow the complete treatment regimens or with insufficient treatments is another factor contributing to antimicrobial resistance. To control and treat tuberculosis, early detection is important which on the other hand requires accessibility to the rapid and efficient diagnostic tools which is difficult to approach in many areas around the world. The major challenge while the treatment of drug resistance TB is started is the adherence to the treatment and the tolerability of the treatment (Sulaiman & Lam, 2021). As a result of gene mutation and structural changes in Mycobacterium genome make the available drugs useless for treatment. Resistance is a major challenge as it complicates the treatment and preventive measures especially in individuals with HIV co-infection (Soko et al., 2021).

Types of Resistance

Two majorly found types of resistance include genetic resistance and phenotypic resistance (Batt et al., 2020). The mechanism of resistance followed by *M. tuberculosis* includes intrinsic resistance and acquired resistance (Figure 2).

Intrinsic Resistance

Mycobacterium has a characteristic cell wall structure containing complex structure of mycolic acid, this feature of the cell wall makes the

bacteria less permeable for many drugs and therapeutic agents (Alderwick et al., 2015). If the bacteria are continuously exposed to therapeutic agents with low dosage rates, this situation results in the activation of transporter proteins which ultimately develop the irreversible phenotypic resistance. This situation further worsened by the development of severe genetic resistance (El Meouche et al., 2016). Due to the presence of β-lactamase enzymes, bacteria inhibit the effects of β-lactam antibiotics, resulting in resistance against these drugs (Schoonmaker et al., 2014). Bioinformatics analysis of the Mycobacterium membrane shows the presence of efflux pumps. These efflux pumps play a significant role in the mechanism of action of intrinsic resistance in Mycobacterium (Willers et al., 2017).

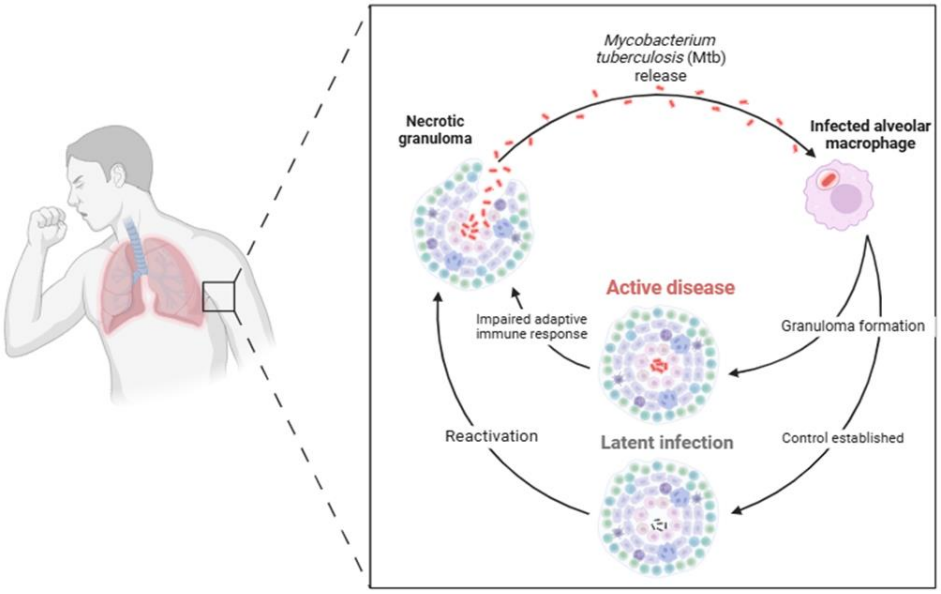

Fig. 1: Pathogenesis of tuberculosis (Active TB disease and latent infection of TB).

Acquired Resistance to TB drugs

As the treatment proceeds, the chromosomal mutation of the gene targeted by the drug occurs which leads to the development of acquired resistance in bacteria (Segala et al., 2012). Development of these resistant mutants is a consequence of different reasons which mainly include lengthy treatment, prescribed drugs not used regularly by the patients, shortage of medication, and poverty especially in low income countries (Cegielski et al., 2014). All these factors result in the resistance to commonly used drugs against TB (Nessar et al., 2011). Use of less effective or ineffective drugs or use of drugs at low dose rate during the course of treatment provide the bacteria with another advantage that is to survive and choose the resistant strain for multiplication. This condition leads to mutagenesis which further results in the enhancement of drug resistance ultimately resulting in multiple drug resistance (van Ingen et al., 2012).

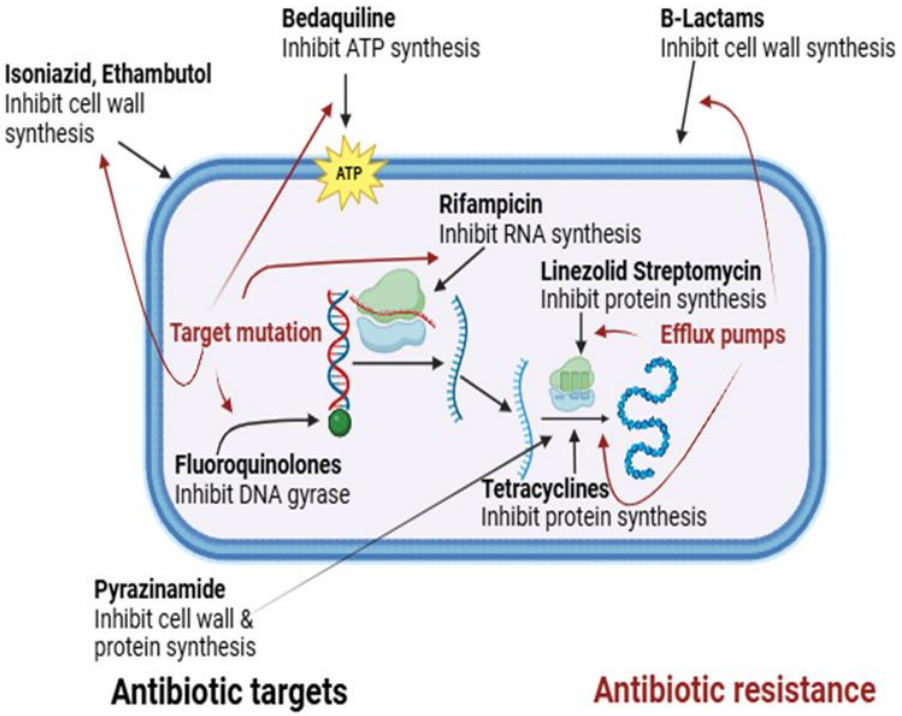

Fig. 2: Resistance of antibiotics in *M. tuberculosis* and mechanism of action.

Risk Factors Associated with Drug-resistant Tuberculosis

The most important factors that independently related to the drug-resistance of TB includes diabetes mellitus, intravenous drug use and previous TB treatment (Gomes et al., 2014).

Diabetes Mellitus

For centuries there has been a recognized link between diabetes mellitus and TB. The evidence proves that diabetes mellitus is a significant risk factor for TB (Alisjahbana et al., 2007; Baker et al., 2011) which can change the course of disease and affect the response to treatment (Dooley & Chaisson, 2009; Mi et al., 2013). Although the mechanism through which diabetes possibly helps in the development of drug-resistance TB is not clear, it is thought that the low absorption of drugs in diabetic patients which decreases the effect of treatment is a possible way to develop resistance (Mi et al., 2013). Just like the anti-TB drugs affect the diabetes treatment, the same is done by the diabetes as it changes the pharmacokinetics of anti-TB drugs. Diabetes affects the treatment by changing rate of oral absorption, decline the protein binding capacity of drugs and significantly renal insufficiency which result in faulty drug clearance (Dooley & Chaisson, 2009). It also causes fatty liver which then results in hepatic toxicity. Hepatic toxicity is a potential source of sub-therapeutic levels of drugs and finally acquired drug resistance (Harries et al., 2011). So it might be possible that resistance is a result of the fact that diabetic patients do not follow treatment regimens for a long period of time.

Intravenous Drug users

Studies have found that intravenous drug use is also a vital risk factor for drug resistance in tuberculosis (Casal et al., 2005; Mdivani et al., 2008). The possible reasons for that include delayed diagnosis, low adherence rate to treatment, and faulty treatment (Duarte et al., 2011). It has been demonstrated in many researches that use of drugs have deleterious effects on the immune system. This fact is associated with physiological effects of drugs and behavior of the individuals as all these factors are involved in developing poor outcomes (Deiss et al., 2009).

Previous TB Treatment

A well-known risk factor for developing drug resistance is previous TB treatment (Yang et al., 2010). Drug-resistant TB can be transmitted between individuals known as primary resistance, most cases of resistance developed due to insufficient treatment which makes drug-resistant strain become more dominant (Suarez-Garcia et al., 2009). To enhance the adherence of treatment directly observed therapy (DOT) is highly recommended (Liu et al., 2013). Studies reveal that the TB patients under DOT have less chances to develop or transmit resistance (Flora et al., 2013).

Diagnostic Methods

WHO has recommended a variety of diagnostic techniques which are currently available for the detection of resistant isolates of *M. tuberculosis* which has been used at different levels in the TB laboratories network. Drug susceptibility testing (DST) is used to check whether a particular population of *M. tuberculosi*s bacilli is susceptible to a particular range of anti-TB therapeutic agents. Results of a DST that show that a particular strain of *M. tuberculosis* is susceptible to a therapeutic agent means that the treatment of that strain with that particular therapeutic agent has greater chances of success. While a result that shows that a strain is resistant to a particular therapeutic agent means that the treatment will not produce significant results and fail to treat the infection so that another therapeutic agent should be used. This shows that use of a reliable DST will develop effective results against *M. tuberculosis* (WHO, 2024a).

Phenotypic Methods

Phenotypic methods indicate culture methods which involve the ability of the *M. tuberculosis* to grow in a specific media. If the bacteria grow in a media (containing specific anti-TB agent) at a specific concentration this shows that the particular strain of *M. tuberculosis* is resistant while on the other hand if the bacteria is unable to grow in that specific media it means that the bacteria is susceptible to that anti-TB agent (Xu et al., 2020). To perform DST at phenotypic level, the mycobacteria grow in different types of liquid or solid culture media. Most commonly used culture media include Löwenstein–Jensen, Middlebrook 7H10 Agar, Middlebrook 7H11 enriched agar and Middlebrook 7H9 broth. The growth of bacteria can be checked visually in solid media by identifying the specific growth patterns of bacterial colonies while in liquid media growth is checked by automated detection of fluorescence which indicates a reduction in the levels of oxygen tension only if bacteria grow in that medium. Before performing a DST, all positive cultures must be typed for the confirmation of *M. tuberculosis* complex (Madeira et al., 2020).

Molecular (genotypic) Methods

In molecular methods (genotypic), specific DNA mutations in the genome of *M. tuberculosis* which are resistant to particular anti-TB drugs are detected. Molecular methods are more reliable and are considered more advantageous in management of drug-resistant tuberculosis. Some important advantages of molecular methods include speed, high standardization and potential of testing, and less requirements for laboratory biosafety while using these methods (MacLean et al., 2020). Currently these genotypic methods include Xpert MTB/RIF assay and two commercial line probe assays (LAPs), MTBDRplus assay and the Nipro NTM + MDRTB detection kit 2 (WHO, 2024b). The specimens for Xpert MTB/RIF assay include sputum, processed sputum sediment, and selected extra pulmonary specimens from both children and adults (Zong et al., 2019). The use of LPAs especially directly on smear positive sputum specimens in routine will improve the time of diagnosis of DR-TB. LPAs help in early detection of drug resistance which ultimately leads to the initiation of relevant treatment which enhances the outcome of the patient's health (Bai et al., 2016).

Treatment Regimens and Challenges

It is not necessary that all the individuals infected with TB will surely develop disease. There are two conditions related to the infection of TB include latent TB infection and TB disease which mainly depend on the strength of host immune responses that whether it is able to fight against the bacteria or not (Ryndak & Laal, 2019). If the immune response against the TB bacteria is weak there are more chances that the bacteria continue to multiply in the body of the host and result in TB disease (Kestler & Tyler, 2022). It is not necessary that the individual exposed to *M. tuberculosis* will develop latent tuberculosis and also not important that the people with latent tuberculosis will surely possess disease symptoms. There are two ways to diagnose latent tuberculosis infection, first is historical tuberculin skin test and second is interferon gamma release assay test. But both of these tests are not necessarily able to differentiate between active and latent infection of tuberculosis (Khabibullina et al., 2022). The best treatment regimen for latent TB which is currently used is a short course of three to four months of rifamycin therapy which was previously nine months of isoniazid monotherapy (Oh & Menzies, 2021). For individuals having resistance against rifamycin therapy, CDC recommended treatment options are six or nine months' therapy with isoniazid, six months if the children or adults are HIV negative and the other therapy is three months of isoniazid plus rigapentine once in week (Sterling et al., 2020). The main advantages of short course therapy is that they have high completion rates and low hepatotoxicity risk as compared to long isoniazid monotherapy (Assefa et al., 2023). It is important to complete the time of treatment as if the treatment is not completed the bacteria can grow again and resistance will develop against that specific drug. Other than lungs, TB can affect lymph nodes, organs, joints and bones and brain. Besides latent TB, the recommended treatment regimen for active TB is the administration of antibiotics for a longer period of time (Assefa et al., 2023). The WHO recommended treatment for active TB involves the administration of antibiotics (more than one) for a period of four to nine months to confirm that all the bacteria are killed (WHO, 2022). Drugs used for TB fall into two categories, first one used for drug-susceptible TB called as first line TB drugs and second one used for drug-resistant TB called as second-line TB drugs (Dartois & Rubin, 2022). The patient may recover from active TB only if they complete the treatment regimen even after the symptoms disappear, under direct observation treatment (DOT) for at least 6 months (Tiberi et al., 2022).

Future Perspectives and Advancement

The drawback of usage of first-line drugs for drug-susceptible TB is the development of drug-resistant TB. The resistance is a consequence of the natural evolutionary process of *M. tuberculosis* bacteria and the standardized treatment regimen (Koch et al., 2018). One of the major challenges for drug-resistant TB treatment is the shortage of rapid and accurate tools for diagnosis as the treatment for drug-resistant TB is far more complicated than that of drug-susceptible TB. A recent study shows that there is a possibility of a massive increase in cases of multi drug resistant tuberculosis between 2015 and 2025 (Kendall et al., 2017). There are several sophisticated diagnostics tools for drug-resistant tuberculosis but their availability is a major concern in many areas and also financial issues are still present in low income communities. The ability of the diagnostic tools to detect mutation outside the defined region and time consuming procedures are other limitations of these diagnostic tools (Nguyen et al., 2019). Research shows that there are almost three million missed cases of tuberculosis every year (Tollefson et al., 2016). The cost of treatment is also a major factor which influences the treatment period of drug-resistant tuberculosis which costs 25 times more than the drug-susceptible tuberculosis treatment (Manjelievskaia et al., 2016).

Conclusion

Drug-resistant tuberculosis is a major obstacle to the elimination of tuberculosis worldwide. Due to drug resistance, the efforts of diagnosis and treatment of TB is failing every year. Previous treatment history, patients with other immunological disorders, lengthy course of treatment, unavailability of diagnostic tools for better diagnosis of the disease, and property of bacteria to go through genetic mutations are the key points which hinder the eradication of tuberculosis. For the better control of TB, more attention and investment in diagnosis and treatment fields is needed to prevent this pandemic. The need for advanced tools for the early detection and diagnosis of the disease (both latent and active) is necessary to control the infection before it spreads drastically in all populations. Inventions are being made to decrease the treatment duration for drug-susceptible and multi drug resistance tuberculosis. WHO recommendations are connecting the gap between implementation and facilities for treatment for all long and short regimens. New drug combinations are under trial to find out a more efficient and shorter treatment regimen.

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