

New Perspective: MDR TB

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Abstract

Background:

Multidrug-resistant tuberculosis (MDR-TB) represents a major global public health challenge due to resistance to key first-line anti-tubercular drugs, namely isoniazid and rifampicin. This resistance complicates disease management, prolongs treatment duration, and increases morbidity and mortality, particularly in resource-limited settings with weak healthcare infrastructure.

Objectives:

This study aims to provide a concise overview of MDR-TB, focusing on its epidemiology, diagnostic challenges, treatment strategies, and emerging approaches for effective control and management.

Methods:

A narrative review approach was employed, synthesizing current literature on MDR-TB epidemiology, diagnostic techniques, treatment regimens, and recent advancements in therapeutic and control strategies.

Results:

The burden of MDR-TB varies geographically, with higher prevalence in low- and middle-income countries. Conventional diagnostic methods, such as culture and drug susceptibility testing, are time-consuming, whereas rapid molecular diagnostics have improved early detection and resistance profiling. Treatment regimens for MDR-TB are prolonged (18–24 months) and rely on second-line drugs that are less effective, more toxic, and costly, leading to challenges in patient adherence. Recent developments, including novel drugs, shorter treatment regimens, and improved diagnostic tools, demonstrate promising outcomes in enhancing treatment success and reducing transmission.

Conclusion:

MDR-TB continues to pose a significant threat to global tuberculosis control. A comprehensive and integrated approach—combining rapid diagnostics, effective and shorter treatment regimens, and strengthened healthcare systems—is essential to curb the spread and impact of MDR-TB and improve patient outcomes.

Key words: MDR TB, Drug resistance, Isoniazid, Rifampicin

Introduction

Tuberculosis has roots in human history dating back to ancient times. On March 24, 1883, Robert Koch identified *Mycobacterium tuberculosis* as the causative agent of tuberculosis. TB is rampant and a major health concern nowadays. The World Health Organization declared TB a global emergency in 1992. Tuberculosis is the leading cause of death globally. *Mycobacterium bovis* and *Mycobacterium africanum* also cause TB worldwide. It is a type of airborne disease caused by bacteria that involves the respiratory system. Around 20% (1 billion, approx.) of the world's human population is infected by it, which causes 3 million deaths per year. In the US, this disease occurs most commonly among the elderly, homeless, malnourished, or alcoholic poor males, minorities, prison populations, immigrants, morticians, and Native Americans (Willey et al., 2008). In past years, the incidence of tuberculosis drug resistance has increased rapidly, which threatens the ultimate goal of ending the TB pandemic. The strain *Mycobacterium tuberculosis* shows resistance to the antibiotic rifampicin and isoniazid (Ormerod, 2005b). Antibiotics are synthetic compounds created to target and eliminate specific bacterial strains, but they are ineffective against various other pathogens and certain bacterial species. Mutations in the *katG* or *inhA* genes lead to isoniazid resistance, while alterations in the *rpo* gene's beta subunit cause rifampicin resistance. These distinct genetic mutations must occur separately for tuberculosis to transition from being susceptible to drugs to becoming multidrug-resistant (MDR-TB). A concerning development is the consistent increase in antibiotic resistance within traditionally susceptible bacteria, underscoring the urgent need for the development of

advanced antibiotics and novel drug classes. In comparison to tuberculosis, MDR TB treatment is expensive, longer, poorly tolerated, and has a very low success rate (“Multidrug Resistance Tuberculosis,” n.d.-b).

Drug Resistance Terminology

MDR TB stands for Multidrug Resistance Tuberculosis which is resistant to isoniazid and rifampicin, and practically incurable by standard first-line treatment.

XDR TB stands for Extensively Drug Resistant Tuberculosis which is resistant to isoniazid, rifampicin, a fluoroquinolone, and a second-line injectable (amikacin, capreomycin, and kanamycin) drugs.

XXDR TB is resistant to all drugs (Seung et al., 2015).

Mechanism of Drug Resistance

One of the major impediments to the treatment of tuberculosis is drug resistance, the intrinsic drug resistance observed in *Mycobacterium tuberculosis* has conventionally been ascribed to the distinctive structure of its cell wall, which contains mycolic acid. This structural feature imparts the bacteria with low permeability, limiting the effectiveness of various compounds, including antibiotics and other chemotherapeutic agents (Jarlier & Nikaido, 1994). In recent times, there has been a growing acknowledgment of the significance of efflux mechanisms in contributing to the inherent resistance of mycobacteria against antibiotics like tetracycline, fluoroquinolones, and aminoglycosides, among others. (De Rossi et al., 2006)

Table 1: Drugs, Minimum Inhibitory Concentrations (MICs), and Mechanisms of Drug Resistance

Drug	MIC (mg/L)	Gene	Role of Gene Product
Isoniazid	0.02–0.2 (7H9/7H10)	katG	Catalase/Peroxidase
		inhA	Enoyl Reductase
		ahpC	Alkyl Hydroperoxide Reductase
Rifampicin	0.05–0.1 (7H9/7H10)	rpoB	β-Subunit of RNA Polymerase
Pyrazinimide	16–50 (LJ)	pncA	PZase
Streptomycin	2–8 (7H9/7H10)	rpsL	S12 Ribosomal Protein
		rrs	16S rRNA
		gidB	7-Methylguanosine Methyltransferase
Ethambutol	1–5 (7H9/7H10)	embB	Arabinosyl Transferase
Fluoroquinolones	0.5–2.0 (7H9/7H10)	gyrA/gyrB	DNA Gyrase
Kanamycin/Amikacin	2–4 (7H9/7H10)	rrs	16S rRNA
Capreomycin/Viomycin	2–4	tlyA	rRNA Methyltransferase
Ethionamide	10 (7H11)	inhA	Enoyl Reductase
p-Amino Salicylic Acid	0.5 (LJ)	thyA	Thymidylate Synthase A
PA-824 and OPC-67683	0.03 (7H9/7H10)	Rv3547	Hypothetical 16.4 kDa
TMC207	0.03 (7H9/7H10)	atpE	ATP Synthase

This table presents information on various drugs used in the treatment of tuberculosis, their corresponding Minimum Inhibitory Concentrations (MICs), the associated genes, and the roles of the gene products in drug resistance. The references provide sources for further details on these drug-resistant mechanisms (Da Silva & Palomino, 2011).

Epidemiology

The World Health Organization (WHO) has investigated the magnitude of the multidrug-resistant tuberculosis (MDR-TB) issue through cross-sectional surveys. These surveys have been conducted in either clinical series or entire-country cohorts, providing valuable insights into the prevalence and scope of drug resistance (Coker, 2001). The Global Tuberculosis Report 2023 by the World Health Organization (WHO) highlights significant findings regarding the prevalence of multidrug-resistant tuberculosis (MDR-TB):

- Annually, approximately 470,000 individuals contract MDR-TB. Tragically, around 180,000 lives are lost each year due to MDR-TB, underscoring the severity of this global health challenge (World Health Organization: WHO, 2021)
- In new cases of tuberculosis (TB), the prevalence of multidrug-resistant TB (MDR-TB) is estimated to be less than 4% in the WHO African, South-East Asian, and Western Pacific regions, while it reaches up to 26% in the European Region. Among individuals with a history of TB treatment, MDR-TB prevalence ranges from 7.9% in the Eastern Mediterranean Region to as high as 57% in the European Region. These variations emphasize the regional differences in the burden of drug-resistant TB(2.3 Drug-resistant TB, n.d.)
- In 2019, the global burden of multidrug-resistant tuberculosis (MDR-TB) was significant, as highlighted by key indicators:
 1. The estimated number of MDR-TB cases worldwide stood at 687,839.
 2. The age-standardized prevalence rate (ASPR) was reported at 8.26 per 100,000 population.
 3. Disability-adjusted life years (DALYs) attributed to MDR-TB were reflected in an age-standardized rate of 52.38 per 100,000 population.

The age-standardized death rate (ASDR) resulting from MDR-TB was documented at 1.36 per 100,000 population. These metrics underscore the substantial global impact of MDR-TB in terms of prevalence, disease burden, and mortality rates (Lv et al., 2024).

These statistics underscore the gravity of the global health challenge posed by multidrug-resistant tuberculosis (MDR-TB). It emphasizes the critical need for ongoing efforts dedicated to preventing, diagnosing, and effectively treating MDR-TB to mitigate its impact on individuals and communities worldwide(Programme, 2023).

Diagnosis

The successful diagnosis and treatment of MDR-TB rely on timely and accurate drug sensitivity testing (DST), which helps in selecting the most effective drug. DST (Lowenstein-Jensen medium) encompasses phenotypic tests that observe bacterial growth or metabolic inhibition in media with and without anti-TB drugs and molecular tests that identify genes associated with drug resistance (Jang & Chung, 2020). Phenotypic DST, a conventional method, employs solid culture media such as egg-based or agar-based materials. Three main techniques are utilized: the proportion method, the resistance ratio method, and the absolute concentration method.

1. The proportion method is the most widely used and is considered the reference standard for assessing bacterial susceptibility to drugs.
2. The absolute concentration method is also commonly employed due to its practicality. These methods are highly sensitive, clinically relevant, and capable of determining minimal inhibitory concentrations. Nevertheless, they are time-consuming, often taking 2 to 3 months to confirm DST results due to the extended duration required for MTB culture (Schaberg et al., 1995).

Liquid culture and DST boast a heightened efficacy in isolating MTB and faster detection compared to solid culture and DST methods. However, their implementation involves increased expenses and a potential risk of heightened bacterial contamination and cross infection from nontuberculous mycobacterial isolation (*Publications Detail*, n.d.-b). To accelerate mycobacterial culture and drug sensitivity testing (DST), a versatile rapid culture method has been devised, utilizing liquid media like BACTEC 460, Mycobacteria Growth Indicator Tube (MGIT), Septi-Check, Myco-ESP Culture System II, and BacT/ALERT MB susceptibility kit. These approaches have the capacity to provide DST outcomes within a month, markedly reducing the time required compared to traditional methods. (Koh et al., 2012) Two widely utilized liquid-based culture systems are the BACTEC 460, which identifies carbon dioxide production, and the MGIT, recognized for its ability to detect oxygen consumption. Liquid culture techniques, while beneficial in some respects, do have drawbacks. They can be prone to undetected contamination, heightened proliferation of non-tuberculous mycobacteria (NTM), and reliance on expensive, complex systems (Lawson et al., 2013). Additionally, these methods often demand highly trained staff and specialized, high-level biosafety facilities, which restricts their utility, especially in regions with limited resources or lower-income settings.

Hence, numerous nucleic acid-based assays have emerged, aiming to detect mutations linked to drug-resistant tuberculosis (DR-TB). These assays are designed to offer cost-effective, precise, uncomplicated, and swift diagnostic tests for identifying DR-TB cases.

Molecular assays for the detection of drug resistance TB:

DNA line probe assays

Line probe assays (LPAs) are DNA–DNA hybridization assays designed to detect various mutations concurrently by employing multiple probes (Mäkinen et al., 2006).

). After DNA extraction and target amplification, amplicons are hybridized to specific oligonucleotide probes that are complementary to the target sequences and are immobilized on the surface of a strip. After several post-hybridization washes to remove the non-specific binding, the amplicon-probe hybrids are visualized by the eye as colored bands on the strip. The turnaround time of the whole assay is 5–7 hours (Mitarai et al., 2012)

Real-Time PCR Assays

Real-time PCR has become widely adopted in the development of rapid diagnostic tests. It operates through two primary methods:

1. Utilizing non-specific fluorescent dyes to detect double-stranded DNA formed during PCR amplification.
2. Employing sequence-specific probes labelled with a fluorescent reporter to identify the hybridization between probes and amplicons accurately. Each probe possesses a specific melting temperature (T_m), and any change in T_m indicates the presence of mutations in the target.

These attributes have been leveraged to create real-time PCR tests specifically tailored for screening drug resistance.

Sequencing

Sequencing stands out as one of the most effective technologies for swiftly analyzing an organism's genotype. Alongside targeted gene sequencing (TGS), the advent of Next Generation Sequencing (NGS) marks a significant milestone in molecular biology. NGS has revolutionized the field by swiftly offering comprehensive whole-genome data in a single run (Manson et al., 2017)

Treatment

The primary objective of treating Multi-Drug Resistant Tuberculosis (MDR-TB) is to achieve a complete cure for the affected individual while simultaneously preventing the transmission of MDR-TB to others. The World Health Organization (WHO) recently issued updated guidelines for treating multidrug-resistant tuberculosis (MDR-TB), introducing significant recommendations to enhance patient care and treatment efficacy:

1. 6-Month BPaLM Regimen:

Recommended for patients with MDR-TB, including those with additional resistance to fluoroquinolones (pre-XDR-TB).

The BPaLM regimen comprises four essential drugs: Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin. Administered over a span of 6 months.

2. 9-Month All-Oral Regimen:

Proposed as an alternative for MDR-TB patients without fluoroquinolone resistance.

Eliminates injectable agents, incorporating solely oral medications.

3. Other Noteworthy Recommendations:

In-depth coverage of treatment regimens tailored for isoniazid-resistant TB, extended all-oral protocols, monitoring treatment responses, and optimal timing for antiretroviral therapy (ART) for MDR-TB patients co-infected with HIV.

The guidelines also delve into surgical options for individuals undergoing MDR-TB treatment.

These updated guidelines underscore a commitment to improving treatment outcomes and patient care in the realm of drug-resistant TB. The advancements are grounded in the latest evidence and research, showcasing a dynamic approach to tuberculosis management. (Programme, 2022)

Adverse effects and treatment challenges

The effective application of first-line drugs in the treatment of drug-susceptible tuberculosis (TB) has led to a new challenge: the emergence of drug-resistant TB (DR-TB). This development is a consequence of the natural evolutionary process of *Mycobacterium tuberculosis* (MTB) and the uniform treatment approaches applied irrespective of the location of emergence, severity, pathology, or comorbidities (Koch et al., 2018b)

The emergence of drug-resistant tuberculosis (DR-TB) has led to treatment challenges due to the complexity of managing DR-TB compared to drug-susceptible TB. According to the WHO Global Tuberculosis Report 2018, the success rates for DR-TB treatment in 30 high TB burden countries ranged from 48% to 86%, averaging at 56%. Notably, India, Indonesia, Mozambique, and Ukraine reported the lowest success rates, indicating the need for improvements in the standardized protocol for DR-TB treatment. (*Global Tuberculosis Report 2013*, n.d.) This finding indicated that there is still room for improvement in the standardized protocol for DR-TB treatment. Achieving swift and precise diagnosis poses a challenge in the treatment of drug-resistant tuberculosis (DR-TB). A recent projection study on the emergence of DR-TB suggests the potential for a significant upsurge in cases of multidrug-resistant TB (MDR-TB) from 2015 to 2025. Reinforcing this, data indicates that testing all tuberculosis (TB) patients for resistance by 2017 could have resulted in a 29% reduction in MDR-TB incidence by 2025. (Kendall et al., 2017) Various diagnostic methods for drug-resistant tuberculosis (DR-TB) range from conventional techniques like the traditional culture method to advanced molecular approaches such as Xpert MTB/RIF, GeneXpert, and whole-genome sequencing. However, accessibility to these facilities is hindered by financial constraints and geographic factors. Additionally, these diagnostic tools have limitations, including their inability to detect mutations outside the well-established region (e.g., the rifampicin-resistance determining region in the *rpoB* gene). This limitation is particularly relevant to a small proportion of DR-TB cases, and the diagnostic process is further impeded by its time-consuming nature and the requirement for costly equipment. (Nguyen et al., 2019) Annually, it is approximated that over three million cases of tuberculosis (TB) go undetected.

The extended duration and intricate drug regimen add to the difficulties encountered in the treatment of drug-resistant tuberculosis (DR-TB), impacting patient adherence. Managing multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) typically requires continuous therapy lasting 6–18 months, involving the administration of multiple drugs without interruption. Designing an appropriate drug regimen involves considering the patient's history of prior medications, including the specific doses and durations. (5) In addition to its inherent complexity, the treatment of drug-resistant tuberculosis (DR-TB) encounters a substantial barrier due to the high costs involved. The expenses associated with DR-TB therapy often reach levels that are 25 times higher than those for treating drug-susceptible TB. (Manjelievskaja et al., 2016) Untreated cases often result from a combination of societal stigma, socio-economic burdens (with DR-TB patients typically experiencing income loss due to prolonged therapy), and a lack of awareness. (Gebreweld et al., 2018). Ensuring that patients adhere to their treatment is a crucial element of tuberculosis (TB) therapy. Incomplete adherence increases the risks of treatment failure, disease relapse, heightened transmission, the emergence of more severe drug resistance, and, in some instances, fatal outcomes. (Alipanah et al., 2018) According to findings from a recent trial, the established benchmark for adherence was reaching 76–80% of the intended doses taken by the patient. (Vernon et al., 2019) Various factors, including medication forgetfulness, missing appointments, financial constraints, and lack of available medicine, frequently contribute to patients with drug-resistant tuberculosis (DR-TB) not adhering to the extended treatment regimen. For instance, India reported non-adherence to treatment in over 50% of the patients. (Mekonnen & Azagew, 2018) Beyond the challenges posed by diagnostics and the prolonged treatment duration, the effectiveness of the treatment is further impacted by the occurrence of side effects associated with the drugs. It is imperative to regularly assess and discontinue drug usage within the treatment regimen whenever uncontrolled side effects manifest in patients. These side effects primarily include ototoxicity, nephrotoxicity, hypothyroidism, psychiatric disorders, epileptic episodes, and uncontrolled gastrointestinal disturbance. (Yang et al., 2017) Discovering a highly effective drug with minimal side effects for the treatment of drug-resistant tuberculosis (DR-TB) faces numerous hurdles, largely tied to the physiological characteristics of *Mycobacterium tuberculosis* (MTB). Lead compounds identified through high-throughput screening often falter in the subsequent phase when subjected to testing against the pathogen using a whole-cell MTB assay. This pattern contributes to a substantial failure rate in the drug discovery and development process for this disease. (Machado et al., 2018)

Prevention of MDR TB transmission

Prioritizing the prevention of MDR tuberculosis is paramount for its control and eventual elimination, aligning with the principle that prevention is more effective than cure. Effective tuberculosis (TB) prevention strategies play a crucial role in mitigating the disease's impact on both individual and population levels. These strategies aim to thwart new TB infections, particularly among high-risk groups, and prevent the progression of latent infections into active diseases.

Additionally, TB prevention programs aspire to disrupt the cycle of tuberculosis bacteria transmission within communities. The following outlines key components of TB prevention: (Li et al., 2017)

1. Early Diagnosis and Treatment:

Rapid identification of TB cases and initiation of appropriate treatment are essential.

Implementing drug susceptibility testing to detect drug resistance early on.

2. Adherence to Treatment:

Ensuring patients adhere to the complete course of treatment is critical to prevent the development of drug resistance.

Implementing directly observed therapy (DOT) to monitor and support patients during treatment.

3. Infection Control Measures:

Implementing effective infection control measures in healthcare settings to prevent the transmission of MDR-TB.

Using proper ventilation and respiratory protection for healthcare workers.

4. Isolation of Patients:

Isolating individuals with infectious TB, especially MDR-TB patients, to prevent the spread of the bacteria.

Utilizing negative pressure isolation rooms when available.

5. Contact Tracing:

Identifying and screening individuals who have been in close contact with MDR-TB patients.

Providing preventive therapy to those at risk of developing TB.

6. Health Education:

Raising awareness about TB transmission, prevention, and the importance of completing treatment.

Educating the community about the importance of seeking medical attention for TB symptoms.

7. Incentives for Adherence:

Providing incentives or support for patients to adhere to their treatment regimen, which may include financial assistance, transportation, or nutritional support.

8. Community Engagement:

Involving the community in TB prevention and control efforts, reducing stigma, and promoting early healthcare-seeking behavior.

9. Monitoring and Surveillance:

Regularly monitoring TB cases, treatment outcomes, and drug resistance patterns.

Implementing a robust surveillance system to track and respond to changes in the epidemiology of MDR-TB.

10. Research and Innovation:

Investing in research to develop new drugs, diagnostics, and vaccines for TB.

Exploring innovative strategies for TB prevention and control.

Social economic impact of MDR TB

Stigma and discrimination:

Stigma poses a significant challenge for individuals grappling with multidrug resistant Tuberculosis (MDR-TB) (International Union Against Tuberculosis and Lung Disease, n.d.). It is impacting their ability to access healthcare facilities in their local communities (Isaakidis et al., 2013). The repercussions of this stigma are diverse, encompassing social seclusion, rejection from family, friends, neighbors, and health providers, along with internalized shame, financial instability, and discrimination (Acha et al., 2007).

A study among healthcare providers emphasized that, notably, the primary barriers faced by MDR-TB patients were social in nature, stemming from the stigma attached to the condition rather than purely medical factors. Unlike some other illnesses, MDR-TB lacks the social acceptance and support crucial for patients (Isaakidis et al., 2013c). Reports indicate that MDR-TB patients may willingly distance themselves from their families due to the fear of transmitting the infection (Morris et al., 2013).

The profound impact of stigma extends to severe consequences such as divorce, the cancellation of impending marriages, the breakdown of family relationships, and isolation within the family unit. The reported effects underscore the urgent need for comprehensive efforts to address and mitigate the social stigma associated with MDR-TB, ensuring that affected individuals receive the support and understanding necessary for their well-being and effective treatment. (Baral et al., 2014).

Economic Issues

Multidrug-resistant tuberculosis (MDR-TB) significantly affects patients economically because of the prolonged and intricate treatment process. The challenges arise from difficulties accessing treatment, the distance to healthcare facilities, transportation expenses, and the financial burden of hospitalization (Horter et al., 2014). A study revealed that 23% of MDR-TB patients discontinued treatment due to financial constraints (Kaliakbarova et al., 2013). Additionally, another study found that half of the patients were unable to return to work even after a year of treatment, with caregivers sometimes having to take extended breaks from work. This situation resulted in reduced salaries due to absenteeism, and some income had to be allocated to cover treatment-related costs (Sharma et al., 2014). These findings highlight the substantial economic impact of MDR-TB and underscore the need for interventions to address financial barriers in the treatment process.

Future direction and recommendation

For the future direction of MDR-TB, it is crucial to focus on several key areas. Firstly, continued research and development of new drugs and treatment regimens are essential to combat the growing problem of drug resistance. Additionally, investing in improved diagnostic tools and techniques can aid in early detection and prompt initiation of appropriate treatment.

Furthermore, strengthening healthcare systems and ensuring access to quality care for all individuals affected by MDR-TB is vital. This includes providing comprehensive support services, such as counseling and social support, to enhance patient adherence and overall well-being.

In terms of recommendations, it is important to prioritize infection control measures to prevent the spread of MDR-TB within healthcare facilities and communities. This involves implementing proper ventilation systems, promoting awareness about respiratory hygiene, and ensuring appropriate use of personal protective equipment.

Collaboration between governments, healthcare organizations, researchers, and communities is crucial to effectively address the challenges of MDR-TB. By working together, we can strive towards a future where MDR-TB is better controlled, and individuals affected by this condition receive the care and support they need.

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No potential conflict of interest was reported by the author.

Data availability statement

The data that support the findings of the present study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and legal restrictions.

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