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A Comprehensive Review of Drug-Resistant Tuberculosis: Mechanisms, Epidemiology, and Diagnostic Approaches

Narrative Review

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ABSTRACT

Background: Drug-resistant tuberculosis (TB) is a critical global health concern, with multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains complicating treatment and control strategies. The emergence of resistance in Mycobacterium tuberculosis (MTB) is driven by genetic mutations and improper antibiotic use, necessitating improved diagnostic methods and therapeutic interventions. Understanding the mechanisms, epidemiological trends, and diagnostic advancements is vital for mitigating the spread of resistant TB strains.

Methods: This review examines the molecular mechanisms of drug resistance in MTB, epidemiological data on resistance patterns, and recent advancements in diagnostic methodologies. Information was collected from peer-reviewed articles, epidemiological studies, and WHO reports to assess the transmission, bacterial fitness, and diagnostic efficiency of emerging tools.

Results: Genetic mutations affecting antibiotic targets, efflux pump activation, and host-pathogen interactions contribute to drug resistance in MTB. Epidemiological studies highlight the increasing burden of MDR and XDR strains, with variations in resistance patterns across different regions. Diagnostic advancements, including molecular assays like GeneXpert MTB/RIF and QuantiFERON-TB, have improved early detection and treatment outcomes. However, traditional culture methods remain essential for confirmatory testing and drug susceptibility analysis.

Conclusion: The rising prevalence of drug-resistant TB underscores the need for comprehensive control measures, including rapid diagnostics, strict adherence to treatment regimens, and novel therapeutic strategies. A multidisciplinary approach involving molecular surveillance, public health policies, and antimicrobial stewardship is essential to curb the spread of resistant TB strains.

Keywords: Bacterial fitness, Drug-resistant tuberculosis, Extensively drug-resistant tuberculosis, Multidrug-resistant tuberculosis, Mycobacterium tuberculosis, Transmission dynamics, Tuberculosis treatment.

INTRODUCTION

Tuberculosis (TB) remains a significant global health challenge, with the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains complicating treatment efforts. Mycobacterium tuberculosis (MTB) has evolved various mechanisms to resist antibiotics, leading to concerns regarding disease transmission, treatment efficacy, and public health interventions. Understanding the mechanisms of drug resistance, bacterial fitness, and epidemiological patterns is crucial for developing effective strategies to control TB. While MTB is pathogenic agent of significant morbidity and mortality (1) .

The misuse of antibiotics has significantly contributed to the rise of multidrug-resistant (MDR) Mycobacterium tuberculosis strains. Several measures can help mitigate this issue, including accurate diagnosis, judicious use of antibiotics, appropriate prescription regimens, ensuring patient compliance, and the introduction of novel anti-tuberculosis drugs (2). The presence of drug-resistant mutations in M. tuberculosis strains can impact bacterial fitness, and in the absence of antibiotics, these strains may struggle to compete with susceptible ones (3).

MDR strains resistant to isoniazid and rifampicin, along with extensively drug-resistant (XDR) strains, which also exhibit resistance to fluoroquinolones and second-line drugs, pose a significant challenge in tuberculosis management. This increasing drug resistance represents a critical threat, potentially rendering the disease untreatable (4). The heterogeneity in drug-resistant mutations influences the relative fitness and transmission dynamics of M. tuberculosis, affecting the initial fitness cost of resistance mutations (5).

The discovery of antibiotics in the 1940s revolutionized the management of infectious diseases. Effective tuberculosis control requires strategies such as accurate diagnosis, responsible antibiotic use, adherence to prescribed regimens, minimizing non-compliance, and introducing innovative treatments (6). In 2012, an estimated 450,000 individuals were affected by MDR-TB, caused by M. tuberculosis strains resistant to first-line anti-TB drugs. Understanding drug resistance dynamics is crucial for comprehending host-pathogen interactions and the cellular mechanisms influencing drug-resistant strain survival and spread (7).

Streptomycin, discovered in 1944, was the first effective anti-tuberculosis drug. Subsequently, the British Medical Research Council developed a combination of para-amino salicylic acid and streptomycin, which reduced resistance. In 1965, rifampicin was introduced, shortening treatment duration from 18 to 9 months. The current six-month Directly Observed Treatment Short-Course (DOTS) strategy remains the standard (8).

According to the World Health Organization (WHO), approximately half a million new tuberculosis cases annually are caused by rifampicin-resistant (RIF-R) M. tuberculosis, with 5–8% exhibiting additional resistance to fluoroquinolones and injectable drugs like capreomycin (9). Since its introduction in 1944, streptomycin has played a pivotal role in tuberculosis treatment, while rifampicin has significantly reduced treatment duration. Recent advancements in treatment regimens have achieved cure rates of up to 80%. However, drug-resistant strains continue to pose a formidable challenge to tuberculosis eradication and control efforts (9).

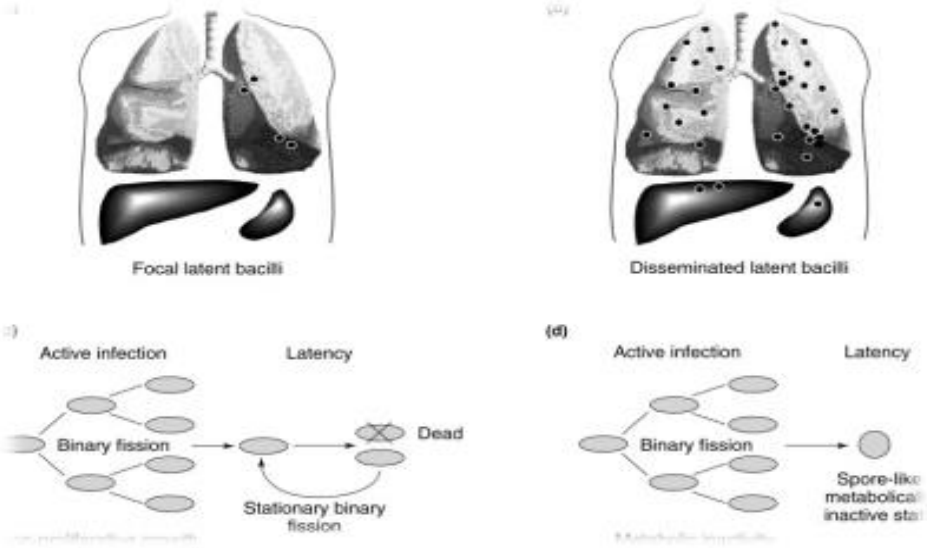
Drug-resistant Mechanism in MTB

Tuberculosis (TB) develops drug resistance through genetic mutations and its ability to survive in hostile conditions, making it increasingly resistant to existing anti-TB drugs. Mutagenic changes caused by reactive radicals enable bacterial cells to evolve and strengthen their resistance. Within the human body, alveolar macrophages and dendritic cells initially engulf TB-causing bacilli, preventing their replication within granulomas (10).

TB bacilli exhibit various survival strategies: (a) they may persist within residual lesions, (b) evade elimination after the initial infection, (c) undergo metabolic breakdown and fragmentation, or (d) transition into a spore-like dormant state, where they remain viable despite an absence of replication or metabolic activity (11).

Inside host phagocytes, Mycobacterium tuberculosis manages to persist by competing for essential metals with Nramp-class divalent cation transporters. A study analyzing the composition of macrophages infected with Mycobacterium tuberculosis strain H37Rv (a wild-type strain) and Mramp-KO (a mutant strain) revealed significant changes in metal concentrations. The levels of phosphorus (P), calcium (Ca), manganese (Mn), iron (Fe), and zinc (Zn) were notably elevated in Mramp-KO, whereas potassium (K) and nickel (Ni) levels

showed a significant decrease. These findings suggest that Mramp is not essential for iron adhesion and retention within the phagosomes of resting macrophages (12).



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Epidemiology

Mycobacterium tuberculosis (TB) continues to evolve, with drug-resistant strains posing a serious global threat to human health. Several factors contribute to the emergence of drug resistance, including inefficiencies in TB management programs, errors in antimicrobial selection, genetic mutations granting resistance, failures in primary prevention measures, and non-compliance with treatment guidelines. In San Francisco, over 95% of TB patients successfully completed therapy, and in the past decade, the proportion of patients initially infected with drug-resistant M. tuberculosis has remained below 15% (13).

Quality control of laboratory diagnostics was primarily conducted through the Supranational Tuberculosis Standards Laboratory Network. Among newly identified TB cases, the median (IQR) rate of resistance to treatment was 11% (ranging from 7% to 23%). While only two cases were reported, the resistance rate in new TB cases varied significantly, from 0% in eight countries to 7% in two regions of China and between 68% and 223% in eight other countries (14).

The transmission dynamics of TB follow a random linear birth-death model, incorporating parameters such as transmission rates, resistance-associated costs, identification percentages, rates of obstruction, and recovery ratios. Genetic marker changes may introduce new genotypes, though not all necessarily result in phenotypic resistance (15). One way to assess the relative transmissibility of drug-resistant versus drug-susceptible TB strains is by comparing secondary attack rates. Researchers analyze secondary infections arising from multidrug-resistant cases compared to drug-sensitive ones (16). Numerous molecular epidemiological studies across various populations have examined the prevalence of resistant and susceptible strains, often comparing these clusters using odds ratios to assess the impact of drug resistance (17).

Retrospective studies have allowed for the comparison of odds ratios between drug-resistant and drug-susceptible TB strains. For example, Alland et al. discovered in early 1990s New York City that nearly half of TB isolates were drug-resistant, with a significant correlation between drug resistance and clustering (adjusted odds ratio 4.52, 95% CI: 0.75–13.01). However, a contemporaneous study in San Francisco found no significant association between clustering and drug resistance, possibly due to variations in resistance histories among isolates. A large-scale study in the Netherlands revealed that isoniazid-resistant strains were less likely to form clusters (odds ratio 0.7, 95% CI: 0.53–0.9), whereas streptomycin-resistant strains exhibited a higher likelihood of clustering compared to susceptible

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strains. These findings highlight that the transmission dynamics of drug-resistant TB vary based on strain properties and epidemiological context (19).

Further analysis of specific genetic mutations has provided additional insights into TB resistance patterns. Researchers observed variations in clustering when analyzing particular mutant alleles, such as the katG Ser315Thr mutation, which differs from other isoniazid resistance-inducing mutations. However, a smaller study found no clustering of strains carrying this mutation, despite its presence in 22 out of 24 isoniazid-resistant Russian isolates within a specific cluster (18).

Diagnosis Approaches

Medical professionals assess tuberculosis-specific cellular immunity using the QuantiFERON®-TB diagnostic test, an advanced experimental tool. This test measures interferon-gamma levels released by activated lymphocytes in whole blood samples when exposed to standard antigens and purified protein derivatives of Mycobacterium tuberculosis. The tuberculin skin test (TST) has been used for decades to detect latent TB infections (20).

Since TB primarily manifests as a pulmonary infection, respiratory TB remains the most common form of the disease. Early symptoms include persistent coughing with sputum production, hemoptysis (coughing up blood), mild fever, night sweats, appetite loss, unexplained weight loss, and fatigue. In addition to pulmonary involvement, TB can also present as lymphadenitis, osteoarticular infections, meningitis, or disseminated (miliary) TB. The clinical signs of extrapulmonary TB (EPTB) vary depending on the affected organs (21).

Laboratory detection of Mycobacterium tuberculosis relies on sputum specimen testing, which can identify mycobacteria even when present in very low concentrations. The sensitivity of smear microscopy requires at least 5,000 acid-fast bacilli (AFB) per milliliter of sample to achieve a 50% probability of detection across 100 observed fields. Culture-based TB diagnosis exhibits over 99% specificity, though confirmatory tests are necessary to distinguish M. tuberculosis from other members of the M. tuberculosis complex. Culturing increases the detection rate by 20% to 30% beyond what smear microscopy can identify, making it an essential diagnostic tool, particularly in cases where sputum smear results are negative despite ongoing infection (22).

M. tuberculosis grows optimally at 37°C within a temperature range of 25°C to 40°C, preferring a pH of approximately 7.0. The bacterium multiplies slowly, requiring a minimum of two weeks for visible growth, with some colonies taking up to eight weeks to mature. On solid agar, M. tuberculosis produces rough, wrinkled colonies with irregular surfaces, initially appearing as small white formations that later develop a yellowish-canary or buff color. Its resistance to emulsification further distinguishes it in culture analyses (23).

In 2007, the World Health Organization (WHO) recommended liquid culture systems for TB diagnosis and drug susceptibility testing (DST). The BACTEC™ MGIT™ 960 system utilizes liquid Middlebrook 7H9 media, continuously monitoring bacterial growth through fluorescence-based oxygen consumption readings every 60 minutes (24). Both the BACTEC 460 and BACTEC MGIT 960 systems play a role in TB diagnosis. However, the MGIT 960 system is preferred for TB management due to its automated, user-friendly, and non-radiometric features, making it a modern alternative to the BACTEC 460 system. While MGIT 960 offers comparable sensitivity to traditional Löwenstein-Jensen culture methods and provides faster results, additional tests are required to confirm M. tuberculosis identification, as it does not facilitate primary mycobacterial detection (25).

The Mantoux tuberculin skin test (TST), also known as the purified protein derivative (PPD) test, has been widely used for nearly a century to screen for TB infection, particularly in developed countries (26). This test involves intradermal injection of PPD tuberculin, with results assessed 48 to 72 hours later based on the presence of induration (≥5 mm). While simple to perform, it requires trained personnel for accurate administration and interpretation. TST is highly effective in detecting TB exposure in low-prevalence populations but may yield false-positive results in individuals vaccinated with Bacillus Calmette-Guérin (BCG) or infected with non-tuberculous mycobacteria. Additionally, TST has limited reliability in immunocompromised individuals (27).

The U.S. Food and Drug Administration (FDA) approved the QuantiFERON-TB (QFT) test in 2001 as an in vitro diagnostic tool for latent M. tuberculosis infection (28). Unlike TST, which requires a two-step procedure with a follow-up visit, QFT provides results from a single blood sample, eliminating the need for intradermal injections. While both tests assess immune responses to TB, QFT measures antigen-induced interferon-gamma production in vitro, whereas TST evaluates a delayed-type hypersensitivity reaction in vivo. Since no definitive test exists to confirm latent TB infection, comparing the efficacy of QFT and TST remains challenging. QFT offers higher

specificity and greater convenience, particularly for individuals with prior BCG vaccination or those requiring routine TB screening. However, neither test alone can conclusively diagnose latent TB without additional clinical information (29).

Recent studies highlight the significant role of W-Beijing genotype M. tuberculosis strains in TB outbreaks and increasing multidrug resistance (MDR). Toungoussova and Caugant (2004) analyzed 55 MTB isolates using the BBL MGIT Mycobacteria Growth Indicator Tube and BACTEC MGIT 960 systems, revealing that drug-susceptible non-Beijing strains exhibited faster growth, whereas drug-resistant non-Beijing strains displayed significantly slower replication (P=0.001). Within the W-Beijing genotype, some drug-resistant strains maintained their original growth rates, while others showed reduced fitness, indicating diverse resistance mechanisms. Further research is needed to understand the biological factors driving the selection and spread of drug-resistant W-Beijing strains (30).

Mariam and Mengistu studied genetic mutations conferring rifampicin resistance in MTB, identifying a mutation rate of 2.3×10^{8} within the rpoB gene. Their research revealed that resistance mutations primarily occur as single nucleotide substitutions at His526Tyr, Ser531Trp, and Ser522Leu positions, further underscoring the genetic basis of MTB drug resistance (31).

The mechanisms by which MTB evades immune detection have been extensively investigated. Vergne and Chua (2004) described how phagocytosis and phagolysosome biogenesis rely on calcium ions, Rab proteins, lipid kinases, and membrane fusion proteins to eliminate pathogens. However, MTB disrupts Rab-mediated membrane transport, preventing proper phagosome maturation and enabling bacterial survival within host cells (32). This inhibition of phagosome-lysosome fusion is a crucial survival strategy for MTB, making it an essential target for developing new therapeutic approaches aimed at restoring normal immune function (33).

Rodrigue and Provvedi (2004) explored M. tuberculosis gene regulation, identifying 13 sigma (σ) factors involved in bacterial RNA polymerase reprogramming. These factors allow MTB to adapt to different environmental conditions and evade host immune responses, highlighting the bacterium's ability to persist in diverse settings (34).

Gagneux and Long (2006) examined the evolution of drug-resistant MTB using mathematical models to predict MDR-TB epidemic patterns. Their findings suggest that rifampicin-resistant MTB strains exhibit varying competitive fitness costs depending on the mutation type and genetic background. Prolonged exposure to antibiotic treatment may ultimately select for MDR strains that not only resist drug effects but also retain or even enhance their fitness in certain environments (35).

Further studies by Rohde and Yates (2007) demonstrated that MTB actively modifies its intracellular environment, maintaining an optimal pH of 6.4 within phagosomes to support bacterial survival. Exposure to concanamycin A significantly disrupted MTB's transcriptional response, highlighting the critical role of pH regulation in its survival strategy. These findings offer potential targets for novel therapeutic interventions aimed at inhibiting MTB resistance mechanisms and enhancing host immune defences (36).

Despite advancements in TB diagnostics and treatment, gaps remain in understanding the genetic mechanisms of drug resistance, host-pathogen interactions, and the transmission dynamics of MDR and XDR strains. There is a critical need for cost-effective, rapid diagnostics, optimized treatment strategies, and targeted public health interventions. Future research should focus on novel drug development, next-generation vaccines, and personalized medicine approaches to improve TB control and prevent the spread of resistant strains.

CONCLUSION

Tuberculosis remains a major global health challenge, with the emergence of multi-drug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains posing significant barriers to disease control. This study highlights the genetic mechanisms underlying drug resistance in Mycobacterium tuberculosis, its epidemiological patterns, and current diagnostic approaches. The increasing prevalence of drug-resistant TB underscores the urgent need for improved diagnostic tools, novel therapeutic strategies, and enhanced public health interventions. Addressing the factors contributing to resistance—such as inappropriate antibiotic use, non-compliance with treatment regimens, and ineffective TB control programs—can help mitigate the spread of resistant strains. While significant advancements have been made in TB diagnostics and treatment, further research is essential to develop more efficient and accessible solutions to combat this growing threat.

Author Contribution

Author	Contribution
Faizan Hameed*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Azka Mubeen	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Arslan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Rohan Arshad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Sidra Iqbal	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ijaz Ahmad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Imad Ud Din Khan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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