IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

The Dual Front of Progress and Challenges in Multi-Drug Resistant Tuberculosis: A Review

Shivam Saxena[1] and Dr. Jitendra Malviya[2]
Research Scholar, Department of Microbiology[1]
Research Guide, Department of Microbiology[2]
Sunrise University, Alwar, Rajasthan, India

Abstract: *Mycobacterium is resistant to battlefront drugs such as rifampicin and isoniazid in MDR-TB. The current global challenge for treatment and diagnosis is imperative due to the fact that over 50% of drugs are resistant. There are five factors that are responsible for MDR as of today: (1) Errors in therapy management by physicians and patients, (2) Complexity and poor vascularization of granulomatous lesions, which obstruct drug distribution to certain sites, resulting in resistance development, (3) Intrinsic drug resistance of tubercle bacilli, (4) Formation of non-replicating, drug-tolerant bacilli within the granulomas, and (5) Development of mutations in Mtb genes, which are the most significant molecular mechanisms of resistance. The most significant contribution of this work is a concise and unambiguous explanation of the factors that contribute to the development of resistance, as well as the most recent diagnostic and treatment methodologies for MDR-TB. This investigation will assist researchers and scientists in the development of alternative swift diagnostic instruments, medicines, and treatment protocols.*

Keywords: Antimicrobial Resistance, Treatment Regimens, Diagnostic Technologies, Public Health Strategies

I. INTRODUCTION

One of the ancient diseases, tuberculosis is caused by a bacterial species called "Mycobacterium tuberculosis" and has a severe impact on the airways. It is the most prevalent organ in which Tuberculosis is developed; approximately 85% of patients with TB experience respiratory complications. However, in the case of tuberculosis, the infectious agent has a propensity to infect any body organ, with the brain, kidney, and spine being the most likely targets.One Infection with tuberculosis bacteria does not necessarily result in illness. TB infection can be classified into two forms: (i) tuberculosis (TB) disease and (ii) LTBI (latent tuberculosis infection) based on these characteristics. The World Health Organization has estimated that nearly two billion individuals worldwide have latent tuberculosis. India is the nation with the highest number of patients who are resistant to multiple drugs. Therefore, drug resistance in tuberculosis is becoming increasingly prevalent. There are also other strains of tuberculosis, which is why the issue of drug resistance is rapidly escalating. As a result of the development of resistance in Mycobacterium strains to pharmaceuticals that are commonly used as first-line treatments, such as rifampin and isoniazid. Therefore, it is imperative to revise the guidelines for resistance development.

What is the meaning of MDR or resistance in tuberculosis?

The global urgent bases are facing a challenge in controlling the growing number of MDR-TB before it spreads to a higher level of pharmaceuticals used in TB. If the patient is infected with TB strains and is resistant to the first-line treatment of medication (antibiotics), the condition is referred to as multidrug-resistant (MDR) TB. Rifampicin and isoniazid are the most efficacious antibiotics and first-line treatments. India (24%), China (13%), and Russia (10%) account for over half of tuberculosis drug resistance. The following are the top three nations. In India, MDR-TB is a prevalent condition that is often caused by the use of incorrect medication and an incomplete TB treatment regimen. Buczynski et al2 and Jen et al3 reported that 58% and (44/72, 61%) of patients, respectively, were experiencing at least one type of error in December 2014 and February 2016. The doses of first-line medications were the most frequently encountered form of error. However, they discovered that 85% of the errors were still inaccurate during the patients'

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

hospitalization. In 2016, the World Health Organization (WHO) advised the use of certain TB drugs in conjunction with intensive chemotherapy for MDR-TB. Mutations that impact the function and expression of chromosome-encoded targets have been associated with resistance to anti-tuberculosis drugs, methods, and molecular techniques. Please provide feedback.Four, five, We updated the most recent information on the diagnosis, treatment, and prevention of MDR-TB.

Objective

To evaluate the most recent advancements in the field of multidrug resistance tuberculosis research.

In order to evaluate and describe the mechanism of drug resistance. the mechanism of drug resistance, and its characterization.

Therefore, the world is acknowledging that MDR-TB is a global issue in the present day. Furthermore, the treatment of MDR-TB is enhanced by a limited number of technologies and strategies that facilitate rapid and precise diagnosis. This review will assist in understanding the most recent technologies and strategies related to MDR-TB. It will be beneficial to establish a commercial use, reproduction, and distribution of the work without requiring additional permission, provided that the original work is attributed in accordance with the new methodology for diagnosis and treatment of global MDR-TB.

Type of Drug-Resistant Mechanism in TB

The extraordinary genetic plasticity of bacteria enables them to combat a diverse array of environmental hazards, as well as the presence of antibiotic molecules that can jeopardize their existence. The growth of microorganisms that share an identical ecological area of interest with antimicrobial-generating organisms has been noted in reports. These mechanisms have been historically developed in microbes to withstand the effects of the environment and the hazardous antibiotic molecule.6

From the evolution perspective, there are 2 pathways responsible for genetic resistance development:

Primary Resistance Pathway—occurs when an individual contracts a strain of tuberculosis that is resistant to antitubercular medications. For example, an individual may contract a mycobacterium that is resistant to the first-line tuberculosis medications by coughing, sneezing, speaking, or singing. In this instance, the individual will not respond to the treatment of these medications. It is imperative to administer novel medications or combinations of medications to them.

The acquired resistance pathway occurs when an individual is infected with a strain that is susceptible to tuberculosis drugs and receives an insufficient treatment, resulting in the development of resistance to drugs due to a mutation in the strain. These forms of resistance are the result of a mutation in the mechanism of (i) antimicrobial targets (which reduces the affinity of drugs for the targets), (ii) drug uptake, (iii) efflux mechanism, and (iv) Mycobacterium metabolic pathways.7 The antimicrobial drug only eliminates the susceptible strain of bacteria for antibiotics once the resistant strain of mycobacterium emerges; however, the resistant strain takes precedence. In numerous instances, these mutant strains result in a reduction in fitness, which is indicative of injury to the cell's homeostasis.

From the general perspective, the following reason is chargeable for multi-drug resistance:

These reasons incorporate all aspects of mycobacterial treatment, including microbiological, clinical, and biological factors that contribute to resistance generation.

Failure to adhere to therapy by the patient and/or the physician's errors in administering the therapy

Resistance development is a result of the poor vascularization and complexity of granulomatous lesions.Nine

Tubercle bacilli intrinsic drug resistance10

The formation of drug-tolerant, non-replicating bacilli within the granulomas.

The primary biological mechanism of resistance is the emergence of mutations in the Mtb gene.

This chapter will provide a more comprehensive explanation of Mycobacterium resistance, including examples (refer to chapters 3.1-3.5).

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

Management errors in the treatment of Mtb

It is the consequence of human behavior and the negligence of humans in their treatment. Poor treatment outcomes are caused by a variety of factors, including acquired drug-resistant tuberculosis. There are the following factors:

Lack of appropriate treatment by doctors and health care providers (treatment without an appropriate guideline or its absence, inadequate training and unskilled nurses and physicians, inadequate patient education and awareness, mismanagement and mishandling of adverse reactions to Mtb drugs, inadequate patient treatment monitoring data, and inadequately funded or organized Mtb control programs).10

Lack of drug supply (problems associated with stock-outs, poor storage conditions, incorrect dose or combination of antibiotics, and inadequate grade of pharmaceuticals and medications).10

Inadequate drug treatment response by patients (malabsorption, adverse effects, absence of understanding of treatment information).10

Complexity of TB granulomas

The complex pathogenesis of Tuberculosis is the result of the lengthy treatment process, which can last from months to a year. An extensive array of heterogeneous granulomatous lesions, ranging from cellular granules that are well vascularized to caseous granules that are avascular, co-exists in both active and latent forms of tuberculosis. The peripheral lymphocytes surround vascularized granules, which contain neutrophils and macrophages. In contrast, avascular caseous granules contain a necrotic center that is caused by the demise of the host cell and the presence of bacteria. The tubercle Bacilli exhibit a spectrum of behaviors in this context, including active replication (AR) stages, which are particularly prevalent in vascularized granules, and latent, sluggish replication (NR) stages, which are particularly prevalent in avascular caseous granules. In animal experiments on rabbits infected with Mtb, it was reported that certain unattached anti-tuberculosis medications penetrate the caseum through passive diffusion. PZA-RIF-INH-EMB are the four medications that are currently efficacious against the intracellular bacilli of AR phases. However, it fails to achieve the same level of precision for the extracellular bacilli of NR stages. The development of drug resistance may be facilitated by temporal and spatial variations in the distribution and accumulation kinetics of medication in lesion-specific behavior.eleven

When caseous granulomas expand, the necrotic centers merge with bronchial airway structures to form pulmonary cavities. These cavities contain both intracellular and extracellular bacilli, as determined by the solubilization of phagosomes in the cavities and liquefied caseum. When exposed to ambient oxygen in the cavity's lumen, these bacilli multiply rapidly. Therefore, the pulmonary cavities exhibit a high bacterial burden.

There is a possibility that a small number of bacteria may endure chromosomal alterations and transmit this mutation to the next generation, thereby developing resistance to the front-line medicine used to treat Mtb.

Intrinsic Mtb drug-resistance

There are numerous positive characters that have been developed as a result of evolution. Mycobacteria also exhibit this characteristic, and they employed Efflux channels, the cell envelope, and other mechanisms to construct intrinsic antibiotic resistance mechanisms (drug degradation, target modification, and general modification mechanism). This mechanism is enabling the bacteria to thrive in environments with high drug resistance.

It can divide into the following section:

Envelope of the cell. The capsule is formed by the cytoplasmic membrane, a network of peptidoglycan (PG), the periplasmic space (PS), the arabinogalactan (AG), and the long-chain mycolic acids (MA) that comprise the mycobacterium cell envelope. Additionally, the capsule is supported by secreted proteins and glycan. Inhibition of MA synthesis is accomplished by INH drugs, while inhibition of AG synthesis is achieved by EMB drugs. Additionally, our first-line TB drug renders Mtb susceptible to other drugs.Twelve

Additionally, it is hypothesized that the hydrophilic layer of AG and PG, which is the innermost, serves to impede the penetration of hydrophobic molecules. Rather, the AG and PG layers are connected to the hydrophobic MA layer at the exterior of the envelope. This layer is composed of long-chain fatty acids and serves to obstruct the entry of hydrophilic medications.thirteen

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

Conversely, these medications are able to enter the cell membrane via passive transport or through its lipid components. The intrinsic form of drug resistance is exacerbated by mutations in the cell membrane components. for instance, Mycobacterium smegmatis that was mutated by the mycolate defective exhibited heightened susceptibility to the first-line drugs RIF, novobiocin, chloramphenicol (CF), and erythromycin.Fourteen

The water-filled porins allow certain small hydrophilic medications to pass through semipermeable membranes without requiring energy. Mycobacterium tuberculosis synthesized a minimum of two porins, OmpA, while rv0899 and rv1698 produced only one porin.Fifteen Nevertheless, the penetration of hydrophilic classes of antibiotics in the category - lactam through the cell wall of mycobacteria was approximately 100 times lower than that of the same antibiotics within the E. coli cell membrane. Therefore, it is presumed that Mycobacteria cytomembrane components, such as - lactam, contribute to the resistance to first-line antibiotic use in the treatment of tuberculosis.16,17 Efflux of drugs. Drug efflux is the term used to describe the process by which medication is expelled from the cell interior to the cell periphery. Cells contain numerous transmembrane proteins that facilitate this process. These are classified into five classes of the ATP-binding cassette (ABC) superfamily based on their energetic and structural characteristics.Eighteen

Major facilitator superfamily (MFS)19

Family of multidrug and toxic compound extrusion (MATE)20

Small multidrug resistance (SMR) familyTwentie

Superfamily of Resistance Nodulation Division (RND)22

ATP energizes the ABC members on one side, which are referred to as primary transporters. On the other hand, secondary transporters, such as MATE and MFS, RND, and SMR, are other forms of transport that obtain energy from the sodium gradient or proton gradient, with the exception of ABC. Nearly 2.5% of the complete genome of the ABC family, SMR family, RND, and MFS superfamilies are comprised of the majority of efflux pumps in Mycobacterium.

The development of low-level resistance is facilitated by the overexpression of efflux pump genes when a medication interacts with Mycobacterium tuberculosis at the sub-inhibitory concentration for an extended period. When an individual receives inadequate treatment for tuberculosis, it develops a high degree of resistance. Several studies have suggested that the overexpression of mmR EP and MmpL7 genes is induced by the exposure of Mycobacterium tuberculosis to first-line medications such as INH.

Additionally, the development of resistance is associated with the quantity of efflux pumps for a variety of drugs.Nineteen

Additional alterations. MDR-TB development is primarily caused by two factors: the first is the cell envelope, and the second is efflux pumps. An additional explanation is the modification of the targeted receptors, the inactivation or modification of the drug's antibodies, the neutralization of toxic substances, and so forth.

For example, the drug-inactivating enzyme, Mtb β-lactamases, is responsible for the sluggish penetration of the semipermeable membrane and has a low affinity for the protein that binds to the penicillin protein of Mtb. It is permissible to develop Mycobacterium that is intrinsically resistant to the majority of β-lactam proteins.13 Mtb is naturally resistant to macrolides as a result of a rRNA methyltransferase and inducible erm (37), which effect ribosomes through methyltransferases 23 srRNA. Magnesium and azithromycin are macrolides.

Phenotypic drug-resistance

Numerous studies have indicated that the Mycobacterium population, which is genetically susceptible but phenotypically drug-resistant, is typically referred to as persisters. This strain is detected in the lung cavities and caseous granulomas of tuberculosis patients. The drug tolerance characteristics of persisters are not heritable and are consistent with their growth, as the concentration of the drug is diminished. The substance remains in place, which allows persisters to survive.

It is frequently classified into two categories based on their accessibility:

1. Class I (Rare)—It is primarily found in replicate populations. They are coatings that are typically resistant to a variety of medications through distinct mechanisms. The use of pharmacological combinations has the potential to eradicate the entire Mtb population.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

2. Class II (Abundant)—It detected nearly all of the cell's populations. For example, in the stationery industry, there is a phase of hypoxia, which results in nutritional deprivation. In order to overcome these circumstances, it is imperative to create a novel antibiotic that is resistant to a wide variety of medications.

Dormancy is the mechanism by which they acquire phenotypical resistance; however, it is insufficient to establish the gap. In numerous other in vitro stress model studies, there are additional characteristics that are crucial for the development of resistance.

In vitro resistance testing is conducted using a limited number of models, which vary in their outcomes depending on the selection. These models include stress models, nutrient deprivation, antibiotic-starved strains, stationary phase, hypoxia (Wayne dormancy model), and acids/nitric oxide gas.ten

For instance, in the Wayne model, quiescent bacilli are acquired through the progressive adaptation of anaerobiosis. The first and second stages have been observed as a result of an oxygen gradient that is self-generated and the NRP (non-replicating persistence). A thickened outer layer was produced by NRP-2 cells, which helped to restrict the entrance of first-line drugs such as RIF.

Acquired drug resistance

A collection of unique medications is implemented to manage tuberculosis. Each drug molecule interacts with at least one or more targets in order to perform its functions, which involves inhibiting the growth of Mycobacterium. As TB treatment remains a concern for an extended period (months to a year), the development of mutations in the targeted sites of clinical strains is accelerated.thirteen

The review reports a specific mechanism that involved the genetic of Mtb to induce this resistance to these medications, such as CP, RIF, KM, INH, and others, on the premise of the primary incidence. The following table provides information on the pharmaceuticals, targeted genes, and gene products that confer resistance to the (WHO groups A, B, and C) in the event of a mutation (Table 1).

Diagnosis of MDR TB

The following scenario was used to diagnose Mycobacterium tuberculosis:

Phenotypic testing is still considered the gold standard and most accurate for Mtb, while drug susceptibility testing (DST) is the earliest. However, this system requires a minimum amount of time to produce results.

Nevertheless, new methods are being devised for the rapid and accurate diagnosis of M. tuberculosis. These methods, which include target gene sequencing, line probe assays, whole-genome sequencing, RIF/Xpert MTB system (USA, Cepheid, CA, Sunnyvale), and DNA/RNA macromolecule amplification devices, are dependent on the identification of the chromosomal mutation.10

As per the 2022 report of TAG,24 the World Health Organization (WHO) recommended the use of Cepheid's Xpert MTB/RIF Ultra in 2020 for the development of new diagnostic assays for non-invasive samples. The Xpert XDR diagnostic technique, which was also released in 2020, is capable of detecting resistance to OFL, KM, INH, AK, and MFX. Several protocols are standardized for the preparation of stool samples in 2021 for molecular testing, including uncomplicated one-step techniques and optimized source flotation.25, 26, and 27 It is less accurate, but stool samples (non-invasive) increase the collection and diagnosis of samples in minors. Due to its specificity of 98.0% and sensitivity of 56.1%. Conversely, samples that are more invasive, such as gastric aspirate, exhibit a higher degree of accuracy in terms of their high specificity (94.1) and sensitivity (70.4%).In 2021, the World Health Organization (WHO) recommended the use of artificial intelligence (AI) for adult diagnosis, utilizing X-ray databases. However, this was not permitted for minors. A number of other non-sputum diagnostics are also promising for the improvement of pediatric MTB diagnosis. These include the TAM-TB blood test from Beckman Coulter and the fingerstick blood test from "Cepheid's Xpert MTB-HR," which is designed to detect the progression of LTBI to active MTB.29,30 The WHO has granted licenses to the commercial reporter gene assays "Nipro NTM+MDRTB detection kit2" and "GenoType MTBDRplus Version 2.0" (Hain Lifescience, Nehren), which were recommended by the TAG as centralized DST. The World Health Organization has approved the use of new centralized determination evolutionary techniques of molecular resistance, and numerous other systems were marketed between 2015 and 2019. these are intended for use in RIF and INH, and these are a few exam-related items. pleas—(i) Roche's Cobas MTB-RIF/INH, which is based in

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

Basel, Switzerland, and (ii) Hain Life Science's MTBDR version 2.0, which is based on the Fluoro type for first-line medications.31

Solutions and Methodology for Treatment for MDR-TB

In recent years, the incidence of Multidrug-Resistant tuberculosis (MDT-TB) has increased in various regions, and it is no longer limited to developing countries. It has also extended to numerous industrialized and established nations. It is crucial to establish new protocols and categories, such as the development of a vaccine against Mtb or monoclonal antibody32, or combinations (such as the use of bedaquiline and pretomanid regimens33,34) of medicine in place of anti-tuberculous first-line drugs, to ensure the effective clinical control and treatment of TB patients, given the new challenging situation of the TB resurgence, which has had a strong impact on the global community and has emerged rapidly.

Table 1. Drugs of TB and affected gene product.

GROUP	DRUG	TARGET GENE/S	GENE PRODUCT (FUNCTION AFFECTED)
A	LFX or MFX	gyrA	DNA gyrase, subunit A (DNA replication)
		gyrB	DNA gyrase, subunit B (DNA replication)
	BDQ	atpE	ATP synthase, subunit FO (ATP synthesis)
		rv0678	Transcriptional regulator (drug efflux)
	LNZ	rp1C	50S ribosomal protein L3 (protein synthesis)
		rrl	23S RNA (protein synthesis)
B	CFZ	rv0678	Transcriptional regulator (drug efflux)
		rv1979c	(Possible permease involved in aminoacid transport)
		rv2535c	(PepQ putative aminopeptidase)
	CS or TRD	alr	Alanine racemase (peptidoglycan synthesis)
c	EMB	embCAB	Arabinofuranosyltransferases (arabinogalactan synthesis)
		ubiA	Phosphoribosyltransferase (cell wall synthesis)
	DLM	ddn	Deazaflavin (F420)-dependent nitroreductase (mycolic acid synthesis)
		fgd-l	Glucose-6-phosphate dehydrogenase (F420 synthesis)
		fbiA	Protein FbiA (F420 synthesis)
		fbiB	Protein FbiB (F420 synthesis)
		fbiC	Protein FbiC (F420 synthesis)
	PZA	pncA	Pyrazinamidase (conversion of PZA into pyrazinoic acid, resulting in dysfunctions of membrane potential)
		rpsA	30S ribosomal protein Sl (m-RNA trans-translation)
		panD	Aspartate decarboxylate (panthotenate synthesis)
		clpcl	ATP-dependent ATP-ase (protein degradation)
	IPM-CLN or MPM	rv2518c	LdtB, nonclassical, L,D-transpeptidase (peptidoglycan synthesis)
		rv3682	PonA2, penicillin-binding protein (peptidoglycan synthesis)
		Rv2068c	blac (ß-lactamase)
	AM	rrs	16S ribosomal RNA (protein synthesis)
	SM	rpsl	ribosomal protein S12 (protein synthesis)
		rrs	16S ribosomal RNA (protein synthesis)
		rrs	16S ribosomal RNA (protein synthesis)
		gidB	(Putative 16S rRNA methyltransferase)
	ETO or PTO	rv0565c	Monoxygenase (activation of pro-drugs ETO and PTO)
		ethA	Monooxygenase (activation of ETO and PTO)

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

		mymA	Monooxygenase (activation of ETO and PTO)
		katG	Catalase-peroxidase (activation of ETO, PTO, INH)
		inhA	EnoyI-ACP reductase (mycolic acid synthesis)
	PAS	thyA	Thymidylate synthase
		folC	Dihydropholate synthase
		dfrA	Dihydropholate reductase

Source: The table has been taken from a paper published by Iacobino et al10.

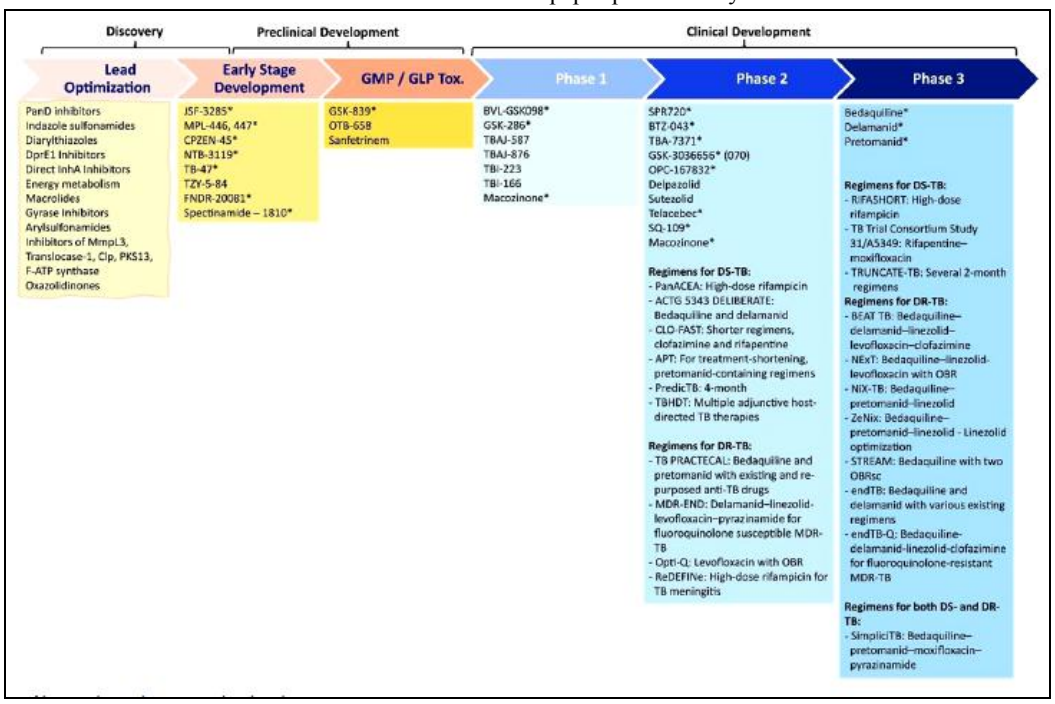

Figure 1. New regimes that are under development.

Complexity of TB granulomas resistance

The formation of a drug gradient into the caseous granulomas, which promotes resistance to Mtb, is the issue related to the Complexity of TB Granulomas mycobacterium resistance (discussed under Section 3.2). The classification of these granules is particularly challenging, particularly in the brain cells. In order to target each type of granule during Mtb treatment, the characterization of granules could be crucial. A metabolomic can be employed to determine the molecular weight of these granules.Thirty- The proteomic instrument can also be employed to analyze the proteins of a variety of complex cellular processes, which is beneficial for drug discovery.36,37 This issue is frequently resolved by combining novel drugs or regimes, such as PZA-RIF-INH-EMB medications, to ensure their efficacy against the AR stages of bacilli in granulomas. Oxazolidinones and ethylenediamine are the new primary compounds that are employed in relation to protein synthesis and multiple pathways, respectively.38 Figure 1 illustrates a few emerging regimes that are currently in the process of being developed.

The utilization of proteomic and metabolomic techniques should be more prevalent in the context of swift diagnostic instruments and treatment methods.

Cell envelope resistance

The inhibitory response of the cell membrane to hydrophobic drugs and mutation into cytomembrane proteins (i.e., porin proteins) are the issues associated with Cell Envelope mycobacterium resistance (discussed in Section 3.3.1). This results in resistance to small hydrophilic drugs. The more lipophilic drug is frequently employed to surmount it, as it has the potential to penetrate a viscous bacterial plasma membrane. Nevertheless, this matter may be more intricate, as

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

certain research advances have indicated that lipophilicity is a critical factor in compound permeability, although it is not the sole factor.39

Phenotypic drug-resistance of Mtb

The issue of drug resistance associated with the phenotype of Mtb (as discussed in Section 3.4) is that persisters serve as a reservoir for evolutionary/mutational processes that enable the primary line drugs to be resistant. Consequently, it is imperative that scientists and researchers pursue the development of a drug that is effective against these persisters (dormant Mtb). Subsequently, it will decrease the duration of tuberculosis treatment and contribute to the reduction of MDR-TB. The combination of Rifapentine and Rifampin at a neutral pH of 7.3 has demonstrated significant results in the elimination of Mtb persisters, as per Lanni et al11 and Iacobino et al40. The dormant Mtb is equally effective against not only one medication, but also the combination of other drugs, such as Nitazoxanide and Rifampin.41 In addition, our research area should encompass a more comprehensive comprehension of the relationship between resistance and persistence, which will facilitate the development of new, innovative, and distinctive medicines and drug combinations to combat and eradicate both categories of bacilli, NR and AR.

Diagnosis improvement

A swift and early diagnostic tool for the Mtb is being developed by researchers who are working day and night. There are several that are currently in the development phase, as indicated below.

MALDI-TOF—Proteomics is a novel field of research that is currently being commercially employed for the diagnosis and treatment of clinical diseases. It is a swift and precise technique that is employed to analyze and detect proteins and organisms. It is beneficial for the detection of all antibiotics, the genotypic analysis of fragmented or specific proteins, the hydrolysis of antibiotics, the presence or absence of bacterial growth, and the internal standard compounds of antibiotics. It is equally employed to diagnose both forms of tuberculosis, whether it is a life-threatening infection or a moderate infection. The results are obtained in a mere 1 to 4 hours, contingent upon the incubation duration of the microorganisms. Depending on the microorganism and the type of resistance, the sensitivity and specificity range from 80% to 100% and 90% to 100%, respectively.42 to 45 Colorimetric tests—The colorimetric method can detect all antibiotics that are resistant or susceptible to the mycobacterium. These arrays facilitate the identification of phenotyping, microbiological growth, antibiotic degradation, and resistant genes to specific antibiotics.

It is beneficial for patients of all levels of severity. Microbial growth can take 12 to 40 hours, which is why there are fewer rapid techniques. Nevertheless, this method has a specificity of 98% to 100% and a sensitivity of 95% for the test specimens.44,46,47 FISH—Fluorescence in situ hybridization—is a technique that employs fluorescence to stain the protein sample and detect it with a smaller beam. It is particularly advantageous for resistance to selective antibiotics, which typically involve ribosomal modifications, such as clarithromycin and linezolid. The FISH is used more frequently to test ESBLs, particularly Campylobacter and Helicobacter species. It is employed to evaluate the test sample of patients who have experienced multiple infections, including respiratory tract, gastrointestinal, and BSIs. The turnaround time is a mere 60 to 90 minutes; however, the test's sensitivity is highly variable. The percentage varies between 80% and 100% depending on the bacterial species. The test has a specificity of approximately 90% to 98%.48,49

Molecular detection system—It is designed to combat the resistant mechanism of numerous antibiotics, which includes a mutation in ribosomes and PB, DNA gyrase, ESBLs, BLs, and resistant related to the permeability and membrane pumps. This mechanism is founded on the principles of nucleic acid (DNA and RNA) amplification. It is extremely beneficial for the rapid identification of colonized patients and health workers. For the detection of test samples, this technique requires approximately 1 to 3 hours and has a sensitivity that ranges from 73% to 100%.Fifty

DNA microarray—This method is predicated on the detection of resistance in respiratory and blood samples through hybridization. A gene sequence array of multiple gene markers of antibiotics, such as ESBLs and Bls, is employed in DNA microarrays. It is particularly beneficial for patients who have experienced multiple infections. The test samples require approximately 2.5 to 8 hours to be analyzed, and the arrays have a sensitivity of 72.9%.45,48

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

Research Gaps, Status, and Feature Trends

The following factors are significant in relation to the most recent antituberculosis drugs:

1. In-vivo testing should be conducted to evaluate the development of long-lasting antibacterial pharmaceuticals and their efficacy. The administration of these medications at extended intervals, patients' compliance, and, as a result, directly observed therapy are all facilitated.
2. Creation of a distinctive compound for MDR-TB is an imperative necessity.
3. The development of a drug for the NR stage of Mtb or slow metabolites Mtb, or, if feasible, for dormant populations of MTB organisms, is a game-changer in the treatment of MDR-TB.
4. In order to overcome the resistance of efflux transporters to medications, scientists should investigate oligonucleotide mimics and PNAs (peptide nucleic acids). The efflux pumps' drug resistance can be overcome by their high specificity of supermolecule binding. We are interested in investigating the potential of additional antibodies as therapeutic agents for M. tuberculosis.
5. The rapid development of 3D protein/drugs for Mtb can be achieved by utilizing advanced and recent bioinformatics/proteomics/genomics technologies.
6. Require the production of medication that is sustainable, despite the potential for minimal commercial benefit to the manufacturing company.

Regrettably, no new medications have been introduced in any of the countries mentioned, with the exception of the United States, for 50 years following the introduction of rifampicin (rifabutin and rifapentine).

There are numerous factors that have discouraged companies from investing in and researching new antituberculosis drugs. The development of novel anti-TB medications is both sluggish and challenging, and the research and development are extremely expensive. Sophisticated, specialized laboratory facilities are necessary to deal with and handle the microorganisms tubercle bacillus. However, there is a limited number of model animals that closely resemble human tuberculosis, which facilitates the research process. This is the reason why the development of any anti-TB drug will be a challenging process and will require a significant amount of time.

The most effective method of preventing MDR-TB is to prevent the progression of normal TB to MDR-TB. Early diagnosis and treatment of MDR TB are insufficient to achieve a cure; additionally, novel and effective pharmaceuticals are necessary.

Currently, over 50% of patients have developed tolerance to MDR-TB due to the use of multiple medications during the treatment of Mtb. It is imperative that the global community remain vigilant regarding the imminent Mtb resistance issue with frontline medications; otherwise, an incident similar to SARS-CoV2 may have occurred.

II. CONCLUSION

Controlling MDR-TB from tuberculosis successfully could be a substantial global challenge and conflict. This review of the literature has provided a comprehensive overview of the microbiological, biological, and clinical issues that support the development of resistance in Mycobacterium. This review paper also reviews all available solutions to combat tuberculosis. A few of them are currently in use in India and around the globe, while others are still in the development stages. These include vaccine development, monoclonal antibodies as medications, and FISH, RDT-based techniques (nucleic acid amplification, microarray), and MALDI-TOF for diagnostic purposes. Even scientists and researchers should prioritize the WGS diagnostic method, according to our assessment. The HRM and WGS method is a highly accurate, sensitive, and convenient technique for scanning for mutations in Mycobacterium. Consequently, it will facilitate the reduction of the cocktail of medications required for treatment and the prolonged exposure to a sub-inhibitory concentration of medication. This initiative will contribute to the reduction of MDR-TB development. In addition to the challenges and solutions of MDR tuberculosis, this paper also briefly discusses the gaps in the research and the actions that can be taken to reduce them. It also discusses the future trend of the researcher in MDR-TB, including the use of proteomics techniques for diagnosis, antibody and vaccines for treatment, and cures. Lastly, this critique substantiated the most recent developments in the mechanisms of drug resistance that have been reported in the past few years in a variety of sources. This review paper also references recent guidelines from the World Health Organization (WHO) in support of international recommendations to facilitate the management of MDR and XDR tuberculosis by microbiologically and clinically equipped facilities on a global scale.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

REFERENCES

[1]. Bloom BR, Atun R, Cohen T, et al. Tuberculosis. In: Holmes KK, ed. Major Infectious Diseases. 3rd ed. International Bank for Reconstruction and Develop- ment. World Bank; 2017.
[2]. Buczynski P, Odenigbo C, Zucker J, Jen SP, Cennimo D, Patrawalla A. 742Eval- uation of anti-tuberculosis medication errors at an urban University Hospital. Open Forum Infect Dis. 2014;1:S209-S210.
[3]. Jen SP, Zucker J, Buczynski P, Odenigbo C, Cennimo D, Patrawalla A. Medica- tion errors with antituberculosis therapy in an inpatient, academic setting: for- gotten but not gone. J Clin Pharm Ther. 2016;41:54-58.
[4]. Oudghiri A, Karimi H, Chetioui F, et al. Molecular characterization of muta- tions associated with resistance to second-line tuberculosis drug among multidrug-resistant tuberculosis patients from high prevalence tuberculosis city in Morocco. BMC Infect Dis. 2018;18:98.
[5]. Migliori GB, Tiberi S, Zumla A, et al.; Members of the Global Tuberculosis Network. MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Net- work. Int J Infect Dis. 2020;92S:S15-S25.
[6]. Kraemer SA, Ramachandran A, Perron GG. Antibiotic pollution in the envi- ronment: from microbial ecology to public policy. Microorganisms. 2019;7:180.
[7]. Munita JM, Arias CA. Mechanisms of antibiotic resistance. Microbiol Spectr. 2016;4:eng1016346142165.
[8]. Strydom N, Gupta SV, Fox WS, et al. Tuberculosis drugs' distribution and emer- gence of resistance in patient's lung lesions: A mechanistic model and tool for regimen and dose optimization. PLoS Med. 2019;16:e1002773.
[9]. Kotze LA, Beltran CGG, Lang D, et al. Establishment of a patient-derived, magnetic levitation-based, three-dimensional spheroid granuloma model for human tuberculosis. mSphere. 2021;6:e0055221.
[10]. Iacobino A, Fattorini L, Giannoni F. Drug-resistant tuberculosis 2020: where we stand. Appl Sci. 2020;10:2153.
[11]. Lanni A, Borroni E, Iacobino A, et al. Activity of drug combinations against Mycobacterium abscessus grown in aerobic and hypoxic conditions. Microorgan- isms. 2022;10:1421.
[12]. Rabaan AA, Mutair AA, Albayat H, et al. Tools to alleviate the drug resistance in Mycobacterium tuberculosis. Molecules. 2022;27: 6985.
[13]. Lange C, Chesov D, Furin J, Udwadia Z, Dheda K. Revising the definition of extensively drug-resistant tuberculosis. Lancet Respir Med. 2018;6:893-895.
[14]. D'Ambrosio L, Bothamley G, Caminero Luna JA, et al. Team approach to man- age difficult-to-treat TB cases: experiences in Europe and beyond. Pulmonology. 2018;24(2):132-141.
[15]. Tak U, Dokland T, Niederweis M. Pore-forming Esx proteins mediate toxin secretion by Mycobacterium tuberculosis. Nat Commun. 2021;12:394.
[16]. Sayed ARM, Shah NR, Basso KB, et al. First penicillin-binding protein occu- pancy patterns for 15 lactams and lactamase inhibitors in Mycobacterium abscessus. Antimicrob Agents Chemother. 2020;65:e01956.
[17]. Kumar G, Galanis C, Batchelder HR, Townsend CA, Lamichhane G. Penicillin binding proteins and lactamases of Mycobacterium tuberculosis: reexamination of the historical paradigm. mSphere. 2022; 7:e0003922.
[18]. Cassio Barreto de Oliveira M, Balan A. The ATP-binding cassette (ABC) trans- port systems in Mycobacterium tuberculosis: structure, function, and possible tar- gets for therapeutics. Biology. 2020;9:443.
[19]. Nasiri MJ, Haeili M, Ghazi M, et al. New insights in to the intrinsic and acquired drug resistance mechanisms in mycobacteria. Front Microbiol. 2017;8:681.
[20]. Machado D, Girardini M, Viveiros M, Pieroni M. Challenging the drug-likeness dogma for new drug discovery in tuberculosis. Front Microbiol. 2018;9:1367.
[21]. Abo-Zeid Y, Amer A, Bakkar MR, El-Houssieny B, Sakran W. Antimicrobial activity of azithromycin encapsulated into PLGA NPs: a potential strategy to overcome efflux resistance. Antibiotics. 2022;11:1623.
[22]. Rodrigues L, Parish T, Balganesh M, Ainsa JA. Antituberculosis drugs: reduc- ing efflux=increasing activity. Drug Discov Today. 2017;22:592-599.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, May 2024

[23]. Hameed HMA, Islam MM, Chhotaray C, et al. Molecular targets related drug resistance mechanisms in MDR-, XDR-, and TDR-Mycobacterium tuberculosis strains. Front Cell Infect Microbiol. 2018;8:114.
[24]. Branigan D, Deborggraeve S, Georghiou S, et al. Pipeline Report » 2022 Tuber- culosis Diagnostics. 2022. https://www.treatmentactiongroup.org/wp-content/ uploads/2022/11/pipeline_TB_diagnostics_2022.pdf
[25]. World Health Organization. WHO Operational Handbook on Tuberculosis. Module 5: Management of Tuberculosis in Children and Adolescents. World Health Organi- zation; 2022. https://www.who.int/publications/i/item/9789240046832 TB-Speed. TB-speed resources. 2022. Accessed October 12, 2022. https://www. tb-speed.com/resources/.
[26]. KNCV Tuberculosis Foundation. The SOS Stoolbox: an implementation pack- age for the SOS stool method to detect TB and rifampicin resistance [internet]. 2022. Accessed September 29, 2022. https://www.kncvtbc.org/en/sos-stoolbox/
[27]. Kay AW, Ness T, Verkuijl SE, et al. Xpert MTB/RIF Ultra assay for tuberculosis disease and rifampicin resistance in children. Cochrane Database Syst Rev. 2022;9:CD013359.
[28]. Sutherland JS, van der Spuy G, Gindeh A, et al. Diagnostic accuracy of the Cepheid 3-gene host response fingerstick blood test in a prospective, multi-site study: interim results. Clin Infect Dis. 2022;74:2136-2141.
[29]. Hiza H, Hella J, Arbués A, et al. Case-control diagnostic accuracy study of a non-sputum CD38-based TAM-TB test from a single milliliter of blood. Sci Rep. 2021;11:13190.
[30]. Medina-Marino A, de Vos L, Bezuidenhout D, et al. "I got tested at home, the help came to me": acceptability and feasibility of home-based TB testing of household contacts using portable molecular diagnostics in South Africa. Trop Med Int Health. 2021;26:343-354.