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An Overview of Multidrug Resistance in Tuberculosis

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Abstract: *The successful human virus Mycobacterium tuberculosis infects one-third of the world's population and kills two million people yearly. This article discusses global tuberculosis (TB) resistance trends, drug resistance pathophysiology, resistance emergence, resistance development, and prevention. Multiple drug-resistant (MDR) and extensively drug-resistant (XDR) strains have exacerbated the global TB issue. These strains are resistant to the most effective drugs and difficult to cure.*

Keywords: Drug-Resistant Strains, Treatment Regimens, Surveillance and Diagnosis

I. INTRODUCTION

One third of the world has TB. Due to drug-resistant strains, TB treatment and control are at risk globally. The WHO's contemporary, short-course TB treatment is a four-drug regimen that depends on patient compliance to assure efficacy. Drug resistance, notably MDR-TB and XDR-TB, is spreading rapidly in new and previously treated patients, necessitating immediate management efforts. MDR-TB is resistant to at least two key anti-TB medications, isoniazid and rifampicin, with or without additional resistance. MDR-TB is harder to treat than drug-sensitive TB and requires less effective second-line anti-tubercular medicines (SLDs) with serious adverse effects.

This brief study summarizes resistance's mechanism and molecular underpinnings. Drug resistance prevention was also stressed.

Tuberculosis, MTB, or TB (short for tubercle bacillus), commonly known as phthisis, phthisis pulmonalis, or consumption, is a common and often deadly infectious illness caused by numerous mycobacteria types. M. tuberculosis1 Tuberculosis usually affects the lungs but may effect other organs. When TB patients cough, sneeze, or otherwise release respiratory fluids, it spreads via the air2. Most latent TB infections are symptomless. One in ten latent infections becomes active, which kills over 50% of individuals afflicted if left untreated.

A persistent cough with blood-tinged sputum, fever, night sweats, and weight loss (thus the name consumption) are the hallmarks of active TB infection. Other organ infections create several symptoms. Chest X-rays, microscopic inspection, and microbiological culture of bodily fluids are used to diagnose active TB. Blood and tuberculin skin tests (TSTs) diagnose latent TB. Treatment is complicated and needs various antibiotics over time. Social interactions are checked and addressed as needed. Multiple drug-resistant tuberculosis (MDR-TB) infections are becoming antibiotic-resistant. Prevention involves screening and bacillus Calmette–Guérin immunization.

One third of the world's population has M. tuberculosis3, with 1% of the population acquiring it annually4. Worldwide, 13.7 million chronic active cases were estimated in 2007. Most of the 8.8 million new cases and 1.5 million fatalities in 2010 were in underdeveloped countries6. Since 2002, new TB cases have dropped, as has the absolute number since 2006. In certain Asian and African nations, 80% of the population tests positive for tuberculin, but just 5–10% of the US population does. Due to HIV infection and AIDS, weak immune systems produce more TB in underdeveloped countries 7.

Signs and Symptoms

The primary symptoms of TB variations and phases are listed8, with many overlapping and some particular to distinct types. Variants may coexist.

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Tuberculosis may infect any bodily part, although it usually affects the lungs. 9. Extrapulmonary TB occurs when tuberculosis grows outside the lungs, yet it may coexist alongside pulmonary TB.
Fever, chills, night sweats, hunger loss, weight loss, and exhaustion are common symptoms. Significant finger clubbing may occur.

Prevention of Tb in Children

The Three I's

Disease prevention is cheaper than treatment. TB prevention is best achieved by preventing its spread. This is done by the Three I's: intensive case discovery, isoniazid preventative treatment, and infection control.

Intensified case finding

Adult TB diagnosis and treatment are insufficient to benefit youngsters. All close contacts and family members, including children, should be checked and treated if symptomatic once an adult has TB. Additionally, HIV-positive children at high risk of TB should be checked often. Treating infected children found during case detection might avert many childhood TB cases.

Isoniazid preventive therapy (IPT)

IPT should be given to all asymptomatic children exposed to TB adults to avoid infection. IPT is crucial for HIV-positive youngsters.

Infection control

Hospitals in high-burden areas may spread TB. Health facilities, households, schools, and other communal spaces must be TB-free. Segregating coughing patients, providing masks, and opening windows and doors for fresh air reduces sickness transmission.
WHO-approved methods successfully decrease childhood TB. Zambian and South African researchers found that improved case finding cut youth TB risk by 50%. Due to resource constraints, many governments don't adopt these tactics. Health care personnel, funding, and training are needed to prevent TB. Country donors should finance bilateral TB programs, UNITAID, and the Global finance to Fight AIDS, Tuberculosis, and Malaria. Additionally, high-burden countries must increase TB budgets and explore additional funding sources like tobacco charges or other taxes.

The fourth I: Integration

HIV impacts the immune system, making TB feasible. TB service integration, or the 'fourth I', is essential for HIV prevention and mother and child health The third leading cause of mortality for AIDS children is TB, which affects over half of HIV-positive children10. Child health care did not previously include TB prevention, treatment, or diagnosis.
TB services for children must be expanded as follows:
Integrated Management of Pediatric Illnesses (IMCI), a comprehensive child health strategy that includes various health facility and community interventions, must include TB treatments and educate and assist health care providers to treat pediatric TB. TB, maternal health, and HIV prevention should be coordinated. WHO and PEPFAR recommend screening all HIV-positive pregnant women for TB 11, 12, 13 since they are 2.5 times more likely to transmit HIV to their unborn child. HIV-positive children are 20 times more likely to get TB than children with strong immune systems, thus they must be tested for both at every health check14.
ART should begin immediately for HIV-positive youngsters. Early ART is the best approach to cut HIV-infected infant mortality and TB risk by 70%.

What Do You Mean By 'Resistant'?

Many 'drug resistance' definitions are ambiguous. M. tuberculosis drug resistance—what is it? Drug resistance is "the ability of certain microorganisms to withstand attack by antimicrobials," according WHO. This indicates >1% of M. tuberculosis bacilli may form in critical medicine concentration. In 95% of untreated wild type bacteria, critical antibiotic dosages stop development. These are epidermiologic cutoffs15. Since the 1930s, antibiotics have had different classes and improved analogs16. These efforts make current antibiotics effective in most clinical diseases except multidrug resistance. Resistance drives antimicrobial R&D. Antibiotic development without resistance reduction is uneconomical and medicinal. Antibacterial progress would suffer without opposition.17.

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Molecular mechanisms of drug resistance

Controlling the epidemic requires understanding how M. tuberculosis develops treatment resistance. This knowledge will help us avoid and discover medication resistance genes. Drug-resistant TB strains may develop from poor therapy or infection with a resistant strain. The frequency of spontaneous mutations in M. tuberculosis that confer anti-TB drug resistance is estimated at 3.5 × 10–6 for INH and 3.1 × 10–8 for RIF. Since drug resistance loci are not linked, the risk of a twofold spontaneous mutation is modest (9 x 10–14) for both INH and Rif18. Prolonged treatment failure is the most common cause of MDR-TB, which resists INH and RIF. Individual first- and second-line drugs will be detailed based on the WHO TB treatment regimen.

Pathogenesis of drug resistance

Each 106 to 108 replications, wild MTB strains naturally develop treatment resistance. The average number of anti-TB mutations is displayed. (Table 1) 19,20 One drug destroys sensitive organisms, reducing TB bacilli and often rendering a person smear-negative. Drug-resistant mutants that survive the initial phase replace the entire population of bacilli with drug-resistant forms that proliferate until they cause symptom recurrence and smear positivity, known as "the fall and rise phenomenon".21. Single-agent treatment with bacillary loads above 106 almost guarantees drug-resistant bacteria. Two drugs may produce resistance if the bacillary load is 108. Bacillary loads exceed 106 with tuberculous infiltrates alone (when sputum direct smears are negative but cultures are positive) and 108 with cavities in TB patients. 22,23

Table 1: Drug versus average muatation rate

Drug	Average mutation rate
Isoniazid	2.56× 10-8
Rifampicin	2.25× 10-10
Ethambutol	1 × 10-7
Streptomycin	2.95× 10-5
Pyrazinamide	1 × 10-6

Modern anti-TB treatment tries to stop drug-resistant mutations. The first treatment regimen should include at least three potentially effective anti-tuberculous drugs to decrease drug resistance to 10-18 or below. The few mutants with spontaneous resistance to one medicine will die more slowly than the "wild type" bacilli that are vulnerable to all drugs during the first treatment. These more resistant bacilli will live longer in the early months of treatment. Drug-resistant mutants will multiply if treatment is terminated early by default, increasing the fraction of drug-resistant forms until they become clinically relevant. Malabsorption (as in HIV-infected people) or insufficient medicine doses have the same impact.

First Line Drugs Used In Tb Treatment

Any anti-TB drug should sterilize and shorten treatment. Current treatment includes INH, RIF, PZA, and ethambutol. At least 10 genes are linked to first-line anti-TB medication resistance: katG, inhA, ahpC, kasA, and ndh for INH, rpoB for RIF, embB for EMB, pncA for PZA, and rpsL and rrs for STR Isoniazid KatG. INH, or isonicotinic acid hydrazide, was synthesized in the early 1900s but identified to cure TB in 195124. INH is activated by katG catalase peroxidase and penetrates cells. In bacterial cells, peroxidase converts INH to a toxic chemical25. This harmful chemical impairs cell wall-related mycolic acid synthesis. Bacteria die from cellular damage without mycolic acid. Middlebrook et al. found catalase loss induces INH resistance26. Genetic studies indicated that katG deletions induce INH resistance and that converting INH-resistant Mycobacterium smegmatis and M. tuberculosis strains with a functional genotype restored susceptibility. In clinical isolates, gene mutations are more prevalent than deletions and may impair enzyme activity. Mutations are most common between codons 138 and 328, especially in katG gene27 codon 315. Ser315Thr was altered in 30–60% of INH-resistant isolates.

The 463 (CGG-CTG) (Arg-Leu) amino acid mutation, the most common katG gene variant, does not induce INH resistance.ahpC. The S315T amino acid mutation decreases katG function but enhances ahpC protein synthesis, which detoxifies toxic organic peroxides. The ahpC gene promoter has five nucleotides that produce over expression and INH resistance28. Ahp C over expression detoxifies organic peroxides and protects bacteria from oxidative damage but not

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INH. Oxidative stress may increase KatG expression. The link between M. tuberculosis INH resistance and ahpC regulatory area polymorphism sites requires more investigation.

inhA.

Activated INH targets inhA locus protein. Enoyl–acyl carrier protein (ACP) reductase29, InhA, may cause INH and ETH resistance. Many studies have connected low-level INH resistance to ETH, a second-line mycolic acid inhibitor. To inhibit mycolic acid synthesis, activated INH forms a ternary complex with InhA-NADH. INH resistance is connected to six structural inhA gene point mutations: Ile16Thr, Ile21Thr, Ile21Val, Ile47Thr, Val78Ala, and Ile95Pro30. The Ser94Ala mutation reduces inhA's NADH binding affinity, preventing mycolic acid synthesis. INH resistance is associated to structural InhA gene mutations, although clinical isolates seldom have them.

InhA promoter mutations are more prevalent at -24(G-T), -16(A-G), -8(T-G/A), and -15(C-T). These promoter mutations overexpress inhA, giving low-level INH resistance. Due to katG and inhA gene changes, 70–80% of M. tuberculosis clinical isolates are INH resistant.

kasA.

The research is divided on whether kasA is an INH resistance target31. This gene produces β-ketoacyl-ACP synthase, which synthesizes mycolic acids. Low-INH resistant gene mutations have been reported. Genotypic study of the kasA gene shows four amino acid changes at codons 66 (GAT-AAT), 269 (GGT-AGT), 312 (GGC-AGC), and 413 (TTC-TTA). However, INH-susceptible isolates had comparable mutations32. However, kasA may be an additional resistance mechanism.ndh. Miesel et al.33 revealed another INH resistance mechanism in 1998. NADH dehydrogenase from the ndh gene forms the ternary complex with activated INH on inhA's active site. Structural investigations demonstrate that reactive INH attacks the NAD(H) co-factor and forms a covalent INH-NAD adduct. NADH dehydrogenase enzymatic activity is impaired by ndh gene mutations. Thus, errors in NADH-to-NAD oxidation cause NADH buildup and NAD depletion. High amounts of NADH may prevent the INH-NAD adduct from attaching to the InhA enzyme's active site. The ndh gene had prominent point mutations at codons 110 and 268 (T110A and R268H) in 9.5% of INH-resistant samples. Mutations identical to these were not found in INH vulnerable individuals 34.

Rifampicin

RIF was launched in 1972 as an anti-TB medicine and sterilizes well 35. The combination of RIF and PZA has reduced standard TB therapy from 1 year to 6 months. Short-course chemotherapy relies on RIF and INH. The fact that mono resistance to INH is frequent while RIF is uncommon is intriguing. Since almost 90% of RIF-resistant bacteria are INH-resistant, RIF resistance may be a proxy marker for MDR-TB 36. RIF inhibits DNA-dependent RNA polymerase transcription. RNA polymerase has four subunits (α, β, β', and σ) encoded by rpoA, rpoB, rpoC, and rpoD genes. Upon binding to the β- subunit, RIF inhibits transcription, resulting in organism death. The rpoB gene in RIF-resistant M. tuberculosis isolates has several mutations and brief deletions, according to extensive research. The report includes 69 single nucleotide alterations, 3 insertions, 16 deletions, and 38 multiple changes37. More than 95% of all missense mutations in the rpoB gene occur in a 51bp core region (Rifampicin resistance determination region) between codons 507–533, with Ser531Leu, His526Tyr, and Asp516Val being the most prevalent. These alterations occur in over 70% of RIF-resistant isolates. The lowest inhibitory concentration (MIC) demonstrated that mutations in codon 526 and 531 cause high RIF resistance, whereas mutations in codon 511,516, 518, and 522 cause low resistance.

Pyrazinamide

The anti-TB action of nicotinamide analog PZA was found in 1952. PZA kills persistent tubercle bacilli in the intense phase of chemotherapy by targeting a fatty-acid production enzyme. During the first two days of therapy, PZA does not kill quickly developing bacilli38. However, PZA sterilizes and shortens chemotherapy from 12 to 6 months. Pyrazinamidase (PZase) encoded by pncA converts PZA, a prodrug, to POA. M. tuberculosis is the only Mycobacterium that PZA affects. Mycobacterium bovis is resistant to PZA owing to a specific C-G point mutation in codon 169 of the pncA gene. An inefficient efflux pump causes POA to concentrate in the cytoplasm, making PZA only effective against M. tuberculosis at acidic pH. POA accumulates and lowers intracellular pH, inactivating a key fatty acid synthase39. Scorpio et al.40 found that M. tuberculosis pncA gene mutations conferred PZA resistance when

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cloning and characterizing the gene. Over 70% of PZA-resistant clinical isolates exhibit pncA mutations, although no mutational hot spot has been found. Peruvian researchers observed 59% of MDR patients had PZA-resistant M. tuberculosis. Many nations do not regularly test PZA susceptibility owing to technological issues. Thus, worldwide PZA resistance is unknown. Louw et al.41 found that drug-resistant clinical M. TB isolates from South Africa are PZA-resistant. PZA resistance was highly connected with MDR-TB, hence it was decided not to use PZA to treat MDR-TB patients. The pncA gene exhibited several nucleotide alterations in PZA-resistant isolates. Mutations in the pncA gene predict PZA resistance. PZA-resistant isolates lacking pncA mutations were also found, indicating another route. Not all mutations (e.g. Thr114Met) caused PZA resistance. Molecular techniques for quick diagnosis are challenging to develop because of PZA resistance complexity.

Ethambutol

Initial mycobacteria treatment EMB is used with other drugs. Cell wall arabinosyl transferase 42 is inhibited by EMB. Telenti et al. found similar arabinosyl transferases in three embCAB genes that resist EMB. Multiple studies show that five codon 306 mutations (ATG-GTG, ATG-CTG, ATG-ATA, ATG-ATC, and ATG-ATT) produce three amino acid alterations (Val, Leu, and Ile) in EMB-resistant strains These five mutations are seen in 70–90% of EMB-resistant isolates. EMB-resistant isolates had missense variants in Phe285leu, Phe330Val, and Thr630Ile. MICs were higher for Met306Leu, Met306Val, Phe330Val, and Thr630Ile strains than for Met306Ile strains. Outside codon 306, rare mutations arise. Johnson et al.43 discovered EMB-resistant embB gene variants at codon 306. Regular phenotypic analysis failed to detect EMB resistance in 91.4% of resistant isolates, confirming EMB testing challenges. TB control suffers from culture-based EMB resistance detection failure. Molecular methods may identify EMB resistance fast, enhancing TB treatment within days. EmpB mutations are absent in 30% of EMB phenotypic resistance isolates. Thus, clinical isolate EMB resistance mechanisms must be recognized.

Streptomycin

WHO recommends aminocyclitol glycoside STR as a first-line anti-TB medication. In TB retreatment, STR is utilized with INH, RIF, PZA, and EMB44. A ribosomal impact of STR has been shown. STR interacts with 16S rRNA and S12 ribosomal protein (rrs and rpsL), causing ribosomal modifications that misread mRNA and impede protein synthesis. INH and RIF are more effective against M. tuberculosis than STR, which is recommended. In 65–67% of STR-resistant isolates, rrs and rpsL genes exhibit point mutations. A C-T transition at sites 491, 512, and 516 and an A-C/T transversion at location 513 were found in the highly conserved 530 loop of the rrs gene. Decoding involves the aminoacyl–tRNA binding site's 530 loop region. The C-T transition at codon 491 occurs in both STR-resistant and susceptible isolates, although it is substantially related with the worldwide expansion of M. tuberculosis with a Western Cape F11 genotype45. Other 915 loop variants [903 (C-A/G) and 904 (A-G)] have been linked to STR resistance.

Second Line Drugs Used In Tb Treatment

Second-line medications include aminoglycosides (kanamycin and amikacin), polypeptides (capreomycin, viomycin, and enviomycin), fluoroquinolones (ofloxacin, ciprofloxacin, and gatifloxacin), D-cycloserine, and thionamides46. Second-line drugs are riskier and less effective. Most MDR-TB therapies use second-line drugs that last 6–9 months. 47. Second-line medicine resistance molecular pathways are listed in Table 3. Molecular and phenotypic methods for second-line drug resistance testing are less established.

Fluoroquinolones

Ciproflaxin and ofloxacin are second-line MDR-TB therapies. Quinolones inhibit DNA gyrase48. DNA gyrase from GyrA and GyrB forms negative supercoils in closed circular DNA molecules. The conserved quinolone resistance-determining region (QRDR) in the gyrA (320bp) and gyrB (375bp) genes49 is where FQ and gyrase interact. Missense mutations in gyrA codon 90, 91, and 94 cause FQ resistance. Resistance improved 16-fold with Ala90Val alterations, 30-fold with Asp94Asn or His94Tyr, and 60-fold with Asp94Gly. The gyrA codon 95 and katG463 polymorphisms divide M. tuberculosis into three evolutionary groups without impacting FQ resistance.

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Aminoglycosides

Kanamycin (KAN) and Amikacin (AMI) are aminoglycosides that restrict protein synthesis but cannot kill latent M. tuberculosis. By binding to ribosomes, aminoglycosides stop bacterial peptide chain elongation. Mutations in 16s rRNA rrs provide KAN and AMI resistance. Rrs gene locations 1400, 1401 and 1483 have nucleotide changes associated to KAN resistance50. An A→G mutation at codon 1400 in the rrs gene caused KAN resistance at MICs exceeding 200 µg/ml.

Ethionamide

MDR-TB is treated with ETH, which works like INH. Like INH, ETH is a bacterial-activated prodrug. The active drug blocks mycolic acid production, preventing cell wall biosynthesis. INH and ETH 51 resistance results from inhA gene promoter mutations.

D-Cycloserine

One of the key molecules of peptidoglycan cross linking is D-cycloserine (DCS), a cyclic analog of D-alanine. DCS competes with D-Alanine for D-alanyl-D-alanine synthetase (Ddl) and Alr enzymes and inhibits their protein synthesis, decreasing cell wall production. Overexpressing alr causes DCS resistance. Overexpression of alr may result from a G→T transversion in the alr promoter. 52.

Peptides

VIO and CAP, basic peptide antibiotics that suppress bacterial protein synthesis, are second-line anti-TB medicines. Earlier investigations have indicated that M. smegmatis' VIO resistance is induced by 30S or 50S ribosomal subunit changes. A G→A or G→T nucleotide mutation at codon 147353 in the rrs gene, which encodes the 16S rRNA, is linked to resistance to VIO and CAP.

Molecular Methods to Predict Drug Resistance

PCR and DNA sequencing are the most common ways to detect drug-resistant TB alterations 54. Regular laboratories cannot use this pricey, skilled procedure.

Probe-based hybridization methods: These assays hybridize drug-resistant gene PCR products to an allele-specific tagged probe that matches the gene's wild type or mutant sequence. To view it, use autoradiography.

PCR-RFLP: Polymorphic DNA sequences are cut with a restriction enzyme and gel electrophoresed to find resistance-associated mutations.

Gel-based single-stranded conformation polymorphism analysis (SSCP) finds 175–250bp DNA stretches. DNA mobility shifts and secondary structural changes produced by minor nucleotide sequence variations are detected via a non-denaturing polyacrylamide gel. Many research have employed PCR-SSCP to find mutational changes connected to M. tuberculosis medication resistance to frontline drugs like RIF and INH 55.

Native gel heteroduplex analysis (HA) requires duplex DNA conformation. Heteroduplexes are formed from heated and re-annealed wild type and mutant PCR products. The wild type and tested DNA strands will form a mismatched heteroduplex if their sequences differ. Current uses of temperature-mediated HA include identifying rpoB, katG, rpsL, embB, and pncA gene alterations. ARMS-PCR, also known as allelic specific PCR (ASPCR) or PCR amplification of specific alleles (PASA), may identify point mutations and small deletions (56). Diagnostic assays may use single-stranded oligonucleotide hybridization probes, or molecular beacons, as amplicon detectors (57). Single nucleotide changes may be detected using molecular beacons. Thus, they are ideal for genotyping and have identified M. TB drug resistance. 58.

How to Prevent Drug Resistance?

The broad objectives of anti-TB treatment are:

Reduce bacterial burden immediately to protect health and reduce mortality.

Prevent drug-resistant mutant strains and

Prevent disease again.

Isoniazid and rifampicin work best for target 1, especially in the first week.

As previously stated, several drugs with proven or suspected efficacy are used to prevent drug-resistant mutant selection.

Long-term treatment with adherence monitoring eliminates remaining live organisms that cause sickness recurrence, achieving the third aim. Rifampicin duration influences this third goal. Many randomized trials support drug-

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susceptible TB dosage, duration, and combinations. Following treatment recommendations and taking all doses attentively is the best strategy to prevent drug resistance.

II. CONCLUSION

Like M. tuberculosis, most antibiotic-resistant bacteria are pathogens that cause worldwide disease. Antibiotic-resistant microbes are continuously emerging, endangering our antibacterial arsenal. Despite treatment failures, longer illnesses, higher mortality, and infection risks, antibiotic resistance must be battled. Global MDR- and XDR-TB cases increasing yearly due to drug resistance.

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