SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 5.
Issue: 3.
Page N. 425-437
Year: 2021

Review Article ww.wjahr.com

PREDISPOSING FACTORS AND DEVELOPMENT OF RESISTANCE TO MYCOBACTERIUM TUBERCULI

Swarna Priya B.*, Tharun Kanduri[1] and P. Chetan Sai[2]

*Doctor of Pharmacy V year, Department of Pharmacy Practice, Jaya College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India.
[1,2]Doctor of Pharmacy IV year, Department of Pharmacy Practice, Sri Venkateswara College of Pharmacy, Madhapur, Telangana, India.

Received date: 03 April 2021 **Revised date:** 24 April 2021 **Accepted date:** 14 May 2021

***Corresponding author: Swarna Priya B.**
Doctor of Pharmacy V year, Department of Pharmacy Practice, Jaya College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India.

ABSTRACT

Tuberculosis (TB) is one of the highly prevalent disease worldwide with the increase in severity and mortality as well. The disease is now a huge public health concern with the effect in association with resistance, resulting in poor health outcomes and huge community spread. The resistance formed makes it more vulnerable towards treatment regimens. This type of resistance can result in multiple drug intake and can poses a greater threat for major health complications as well in future. The current article is built on the different sequences in development of multi drug resistance in tuberculosis and also defines the strategies used to reduce the major public health concern of health outcomes in India.

KEYWORDS: Tuberculosis, Highly Prevalent, Mortality, Community spread, Multi Drug resistance, Health Outcomes.

INTRODUCTION

Tuberculosis (TB), an ancient infectious disease remains a leading cause of morbidity and mortality in developing countries. TB is caused by the bacteria, Mycobacterium tuberculosis which can produce either a silent latent infection or a progressive active disease which usually attack the lungs, but it can attack any part of the body such as the kidney, spine and brain.[1] Emergence of new strains of M. tuberculosis resistant to current anti tubercular drug is the major public health concern that threatens the progress made in TB care and control. Drug resistance in Mycobacterium tuberculosis arises due to improper use of antibiotics in chemotherapy of drug susceptible TB patients or it may also be due to the accumulation of mutations in the drug target genes and these mutations lead either to an altered target or to a change in titration of drug.[2] This review describes the factors contributing for the development of drug resistance, mechanism of resistance to anti-tubercular drugs and discusses on strategies for the prevention of drug resistance.

Over one-fourth of the world population is infected by M. tuberculosis and roughly around 1.4 million people died from active TB in 2019[4], out of which men (aged ≥15) accounted for 56%, women (aged ≥15years) 32% and children (aged ≤15 years) 12%. In 2019, an estimated 10million new cases of TB was reported worldwide. Geographically, most people who developed TB in 2019 were in the WHO regions of south-east Asia (44%), Africa (25%), western pacific (18%), eastern Mediterranean (8.2%), America (2.9%) and Europe (2.5%). Eight countries account for the two-third of the global total: India (26%), Indonesia (8.5%), and china (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%).[5]

In 2019 half a million people developed rifampin resistant TB (RR-TB), of which 78% had multidrug resistance TB (MDR-TB). The three countries with highest share of global burden are India (27%), china (14%) and Russian federation (8%). Nearly 3.3% of new TB cases and 17.7% of previously treated cases had MDR/RR-TB.

Tuberculosis kills close to half a million Indians every year. India now has the greatest number of multi drug resistant TB (MDR-TB) cases in the world, contributing one fourth of the global burden. National anti-tuberculosis drug resistance survey conducted by the Indian government in collaboration with World health

organization (WHO) and the United States agency for Internation development (USAID) showed that nearly 22.4% of newly diagnosed TB patients have resistance to any drug out of this MDR-TB was detected 2.84% of patients, resistance to isoniazid (any 11.06%, monoresistance 3.85%), pyrazinamide (any6.95%, mono 4.11%), streptomycin (any6.88%, mono2.22%) and ethambutol (any 2.28%, mono 0.28%). Mono resistance to rifampicin was not observed among new TB patients. Among previously treated patents 36.82% patients showed resistance to any drugs out of this MDR-TB was detected in 11.62% patients, monoresistance to rifampicin was detected in 0.05%, resistance to isoniazid (any25.09%, mono 7.61%), streptomycin (any13.26%, mono 2.48%), pyrazinamide (any 8.77%, mono4.07%) and ethambutol (any 7.03%, mono 0.21%).[6]

Among the second line agents resistance to Fluoroquinolones (FQ) was highest (21% in non MDR-TB patients and 36% among those with MDR-TB). Higher rates of FQ resistance (24%) were noted in new patients with TB with MDR-TB compared with previously treated TB cases (21%). Aminoglycodide resistance was observed in 7% of new patients with TB and 2% of previously treated cases. Resistance to ethionamide and Para-amino-salicylic acid were 11% each in new patients with TB and 7% and 4% respectively in previously treated patients. XDR-TB was detected in 1.3% of surveyed samples.[6]

A sub national community survey from India, Gujarat, reported XDR-TB in 3.2% of MDR-TB patients. A study in 10 tertiary care centers in 9 cities of India reported 598 isolates of XDR-TB.[7, 17]

The current article describes the etiology, risk factors and various mechanism of action involved in development of MDR in TB patients in regard to individual drugs.

Etiology and risk factors

TB is caused by M. tuberculosis, an aerobic, non-spore forming bacillus that resists decolorization by acid alcohol after staining with basic fuschin thus they are referred to as acid fast bacillus (AFB). M. tuberculosis is transmitted through the air by aerosolization droplet nuclei that are produced when a person with TB cough, sneezes or speak. Droplets may also be produced by other methods such as aerosol treatments, sputum induction, bronchoscopy, endotracheal intubation, suctioning, and autopsy and through manipulation of lesions or processing of secretions in the hospital or laboratory.[8]

Drug resistant TB is prevalent globally and it is the major threat in TB care. The causes of the global spread of drug resistant TB include.

Chaotic treatment: In 1980s and early 1990s there were no standard protocols for the treatment of TB and there was no fixed regimen for the treatment, this led to improper or extensive usage of anti-TB drugs which led to the development of drug resistance. Furthermore, in many settings it was found that TB treatment was not provided for free, contributing to patient noncompliance and development of resistance along with irresistible community spread.[9]

Effect of short-course chemotherapy: As a part of global TB control strategy called DOTS (Direct Observed Treatment Short course) the regimens containing isoniazid and rifampicin became the standard of care. Repeated use of this short course of chemotherapy in poly drug resistance patients resulted in development of resistance to all the first line anti-TB drugs. Kwonjune J Seung et al. performed a retrospective analysis to determine the effect of initial drug resistance on treatment outcomes and acquired drug resistance in new patients receiving standard short course chemotherapy. They reported that pretreatment drug resistance was strongly associated with treatment failure and development of new multidrug resistance.[10]

Community transmission: Recent studies has confirmed that majority of new MDR-TB patients were infected initially with an MDR-TB strain, rather than a slowly acquired resistance caused by inadequate or irregular treatment. Lin et al. performed a study with the aim of identifying mechanisms responsible for the rise in MDR-TB in urban settings. They reported that appearance of resistance may be driven by increased transmission.[11]

Nosocomial transmission: Busy and crowed hospitals and health centers especially in high HIV prevalent settings are the important sites for the spread of MDR-TB. This can result in the spread of drug resistance strains among patients receiving therapy for drug susceptible TB.[9,12]

Gender: according to WHO reports and a population based prevalence survey of TB in Ethiopia, confirmed that, TB was higher among males. This difference might be due to health seeking behavior, environmental factors and higher exposure of males to different factors that poses a risk of acquiring TB.[39]

TB in prison: Prisons are considered reservoirs facilitating TB and multidrug resistant TB (MDR-TB) transmission within the walls, and to the community. Transmission occurs through prison staff, visitors and released inmates. Prisoners come under high risk groups of population. Most of the prisoners come from socio economically disadvantaged population where TB infection and transmission are higher and where access to medical care is limited. Factors that cause infection and progression of the disease include overcrowding, poor ventilation, frequent transfer of prisoners between prisons, late diagnosis and inadequate treatment and weak nutrition etc.[13] According to the WHO report TB cases in prisons may account for up to 25% of a country's burden of TB and High levels of MDR-TB

have been reported from some prisons with up to 24% of TB cases suffering from MDR forms of disease.Few prisoners may self-treat with supplies of anti-TB drugs available through visitors this promote further development of MDR-TB.[14]

Maxwell Drozin et al. performed a systematic literature review to investigate the occurance of MDR-TB in prisons located in Soviet Union. They reported that high prevalence of MDR-TB in prisons of post-soviet states with percentages as high as 16times more than the world wide prevalence estimated by the WHO in 2014.[15]

F. Biadglegne et al. made a systemic literature review to assess the prevalence of drug resistance and risk factors for acquiring TB in the prison population. Their review showed the high prevalence of TB, MDR-TB and XDR-TB in prisons than that found in the general population. Their review also reported that multiple risk factors such as overcrowding, poor ventilation, malnutrition and HIV contribute to spread of TB in prisons.[16]

Other comorbid conditions: Conditions like DM and HIV which impairs the immune system is thought to contribute to the evolution of latent TB infection to active cases and they also contribute to the development of drug resistance in drug susceptible patients. Drug resistance in these patients is mainly due to treatment failures and reinfections.

Antonia Morita Iswari Saktiawati et al performed a retrospective cohort study to analyze the influence of diabetes mellitus on the development of MDR-TB. They reported that patients with TB-DM had 6.8 fold (95%, CI: 2.0-2.37, p+0.003) higher risk of developing MDR-TB.[18]

Jenny-Tyang chang et al. studied the effect of type-2 DM on the clinical severity and treatment outcomes in patients with pulmonary tuberculosis patients with and without type-2 DM (DMTB and TB, respectively). They concluded that DMTB patients have more severe TB infection, higher treatment failure rates and longer delayed clearance of mycobacteria than did the TB patients, which required longer treatment and are more likely to develop MDR-TB when compared with patients with TB alone.[19]

Another study to determine the prevalence of drug resistant TB among people living with HIV (PLHIV) was performed by Neil Saldanha et al. through a multi variable analysis and they determined that TB relapse in HIV patients is the only factor associated with development of MDR-TB, DRTB and INH-mono resistance TB.[20]

Others: Few studies reported that poor treatment adherence and irregular treatment were the strong risk factors for developing MDR-TB. Factors such as psychiatric illness, alcoholism, drug addiction and homelessness may contribute to the non-adherence. Study conducted by Elizabeth Clara Barroso et al. showed that lack of home sewer system, alcoholism, smoking, number of previous treatments, irregular treatment and lung cavities are the factors important for the development of acquired MDR-TB.[24]

Another risk factor is the type of strain that is prevalent in the particular area. Few studies have reported that certain strains of mycobacterium tuberculosis such as Beijing lineage, a genotype associated with enhanced acquisition of drug resistance and increased virulence is associated with MDR-TB and it is also responsible for outbreak of MDR-TB in certain areas.[21,22] A study by Narvskaya et al. showed that W. Beijing genotype contain a specific pathogenic properties such as enhanced transmissibility, ability to cause reinfection and to readily acquire drug resistance to major anti-tuberculosis drug.[23]

Mechanisms of resistance

FIRST-LINE AGENTS

Isoniazid

Isoniazid (isonicotinic acid hydrazide), one of the important drug in the treatment of TB is a prodrug and it must be activated to its toxic form within the bacillus by a gene KatG, a multifunctional catalase-peroxidase, KatG catalyzes the production of isonicotinoyl radical that subsequently interact with mycobacterial NAD and NAPD to produce a adducts. One of these adducts, a nicotinyl-NAD isomer inhibits the activities of enoyl acyl carrier protein reductase (InhA), a complex of an acyl carrier protein (AcpM) and a β-ketoacyl- ACP synthase (KasA). Inhibition of these enzymes inhibits synthesis of mycolic acid; a component of cell wall.[25] Resistance to the isoniazid is associated with the mutation in these genes. The most common mechanism of isoniazid resistance in clinical settings is due to single point mutations in heme binding catalytic domain of KatG, especially a serine to asparagines change at position 315.[32] This type of mutations results in an enzyme that is unable to activate isoniazid. Resistance to isoniazid may also develop due to mutations in genes, encoding for synthesis of mycolic acid (InhA, AcpM, and KasA). The most common InhA mutation occurs in its promoter region (-15C→T) and results in overexpression of InhA. This mechanism confers low level resistance to isoniazid and some cross resistance to ethionamide.[26, 27, 28, 30]

Another adduct, a nicotinoyl-NADP isomer, potentially inhibit mycobacterial dihydrofolate reductase (encoded by dfrA), there by interfering with nucleic acid synthesis.[25] Mutations in drfA genes have recently been shown to be involved in resistance to isoniazid. However studies have failed to demonstrate the role of dfrA in isoniazid resistance.[29]

Other products ofKatG activation of isoniazid include superoxide, H_2O_2, alkyl hydroperoxide and NO radicles;

these contribute to the mycobactercidal effect of isoniazid. Defence against these radicles is provided by alkyl hydro peroxide reductase (encoded by ahpC), which detoxifies organic peroxides.[25] Several studies have found that mutations in promoter region of ahpC gene, leading to its overexpression, this may act as compensatory mechanism for the reduction or loss of activity of the catalyse-peroxidase system.[31]

Studies have also found three novel mutations in the furA-KatG intergenic region, these mutations decreases the expression of KatG and confers resistance to isoniazid.[33] Similar mutations also occur in the intergenic region of oxyR-ahpC;this reduces the expression of InhA and has been associated with resistance to isoniazid.[34]

In summary, mutations in KatG and InhA genes are associated with approximately 70-80% of isoniazid resistant M. tuberculosis isolates. A study by Dalla Costa et al suggest that genetic screening for the S315T KatG mutation may provide information for anti TB regimen selection and for epidemiological monitoring of isoniazid resistance.[35,36]

Rifampicin

Rifampicin, one of the most effective first-line anti tubercular agent, it is also effective against initial isoniazid resistance.[37] rifampicin mainly acts by entering into bacilli in a concentration dependent manner and then binds to the β subunit of DNA dependent RNA polymerase (ropB) to form a stable drug enzyme complex. Drug binding suppresses chain formation in RNA synthesis.[25]

Rifampicin resistance in mycobacterium tuberculosis arises due to the mutations on its molecular target. In 96% of rifampicin resistance cases mutations occur in the codons 507-533 of gene coding for the RNA polymerase β subunit, ropB.[38,39] This region is also known as rifampicin resistance determining region (RRDR). Mutations in codon 531 and 526 are the most frequently reported mutations and results in higher levels resistance to rifampin when compared with resistance cause by mutations in other codons (511, 516, 518, and 522).[40] Few studies have reported that alteration in codons 511, 516, 518 and 522 results in organisms that have low level resistance to rifampin and rifapentine but remain susceptible to two other rifamycins (rifabutin and rifalazyn).[41,42]

Whole genome sequencing studies demonstrated mutations in the ropA and ropC genes, which encode the α and β` subunits of RNA polymerase as compensatory mechanisms in isolates that bear mutations in the ropB gene. These compensatory mutations would be responsible for restoring the fitness of these strains in vivo and have also been associated with a higher transmissibility in some settings.[43]

An important finding related to rifampicin resistance is that, monoresistance to rifampicin is rare and occurs in conjunction with other drugs, most commonly isoniazid. For this reason rifampicin resistance is considered as a surrogate marker for MDR-TB.[44, 45]

Pyrazinamide

Pyrazinamide is the synthetic pyrazine analogue of nicotinamide. Pyrazinamide when used in combination with rifampin shortens the duration of treatment of tuberculosis patient from 1year to 6 months. One key character of the pyrazinamide is its ability to inhibit the semi-dormant bacilli located in macrophages or acidic environment such as TB lesions.[46] Pyrazinamide is a prodrug and it passively diffuses into mycobacterial cells, in which M. tuberculosis pyrazinamidase (encoded by PncA gene) deaminates pyrazinamide to pyrazinoic acid. The pyrazinoic acid is then pumped out of the bacterial cell by weak efflux mechanism. In acidic extracellular milieu, pyrazinoic acid is protonated to a unchanged form which is lipid soluble and re enters the bacillus resulting in cellular damage. Pyrazinamide also targets aspartate decarboxylase (encoded by PanD) involved in making precursor needed for pantothenate and coA biosynthesis in M. tuberculosis.[25] Pyrazinamide also inhibit the ribosomal protein s1 (encoded by RpsA) in the trans-translation process, so that toxic proteins accumulate and kill the bacteria.[47]

Pyrazinamide resistance is mostly caused by mutations in the PncA gene and its promoter region that lead to a loss of pyrazinamidase activity. A study by whitfield et al. reported 608 unique single nucleotide polymorphisms occurred at 397 distinct positions throughout the PncA gene.[48] These mutations account for 72-99% of pyrazinamide resistance.[49]

Few studies reported the mutation in rpsA gene. RpsA gene overexpression is associated with increased pyrazinamide resistance.[50] Whole genome study (WGS) analysis revealed mutations in PanD and indicated that it is necessary to include the screening of PanD mutation to enhance the detection of pyrazinamide resistance.[51] Mutations in PanD decrease the binding affinity for pyrazinamide.

A molecular epidemiologic analysis reported that pyrazinamide resistance is strongly associated with rifampin resistance, conforming the burden of pyrazinamide resistance in patients to rifampicin resistance.[52]

Ethambutol

Ethambutol is the first line agent, used in combination with isoniazid, rifampicin and pyrazinamide in treating TB. It is active against multiplying bacilli. Ethambutol inhibits the arabinosyl transferase 3 (encoded by embCAB), thereby disrupting the transfer of arabinose into arabinogalactan biosynthesis which in turn disrupts the assembly of mycobacterial cell wall.[25] Studies have

shown that embCAB gene was organized as a 10kb operon. Resistance to ethambutol is mediated by mutations in the embB gene.[54] DNA sequencing analysis of 7.5kb region of 10kb embCAB locus suggesting that missense mutations associated with resistance were overrepresented in embB codon 306.[53] It was reported that embB306 mutations predisposes the isolates to develop resistance to increasing number of antibiotics and is not necessarily involved in ethambutol resistance.[55] Lee et al. showed the embB306 mutations in ethambutol isolates of mycobacterium tuberculosis.[56]

Recent studies have confirmed the mutations in embB306 along with mutations in embB406 and embB497 as hotspots for genomic variation in ethambutol resistant isolates.[57] Approximately 30% of ethambutol resistant isolates lack mutations in embB, suggesting the different mechanisms of resistance.

Hassan safi et al. reported the mutations in the decaprenylphosphoryl-β-D-arabinose (DPA) biosynthesis and utilization pathway genes, RV3806c and RV3792 along with mutations in embB and embC resulting in variable MIC range for ethambutol. They also reported that RV3806c mutations cause high level of resistance to ethambutol when they occur with embB and embC mutations.[58, 59]

Streptomycin

Streptomycin is one of the first antibiotics shown to be active against TB. Due to the extensive development of resistance and due to availability of better drug such as isoniazid, rifampin and ethambutol, streptomycin usage was greatly declined. Streptomycin is active against actively growing bacilli and mainly acts by inhibiting the initiation of translation in the protein synthesis. Streptomycin mainly acts by binding to the 30s subunit of the ribosome at the ribosomal protein s12 and 16s rRNA coded by the genes rpsL and rrs respectively.[60, 61]

The genetic basis of resistance to streptomycin is believed to be mediated via mutations in the rpsL and rrs genes, [62]these mutations account for 60-70% of streptomycin resistance. Major mutations that lead to streptomycin resistance occur in rpsL gene, with most common mutations being K43R and K88Q.[63] Most common mutations in rrs genes include alterations in the 530 loop or 915 region.[63]

Few recent studies showed the mutations in gidB, a gene encoding a conserved 7-methylguanosine methyltransferase specific for the 16s rRNA, this confers low level resistance to streptomycin.[64]

SECOND LINE AGENTS

Kanamycin, amikacin, capreomycin and viomycin

Kanamycin and amikacin are the aminoglycoside antibiotics and capreomycin and viomycin are cyclic polypeptide. All the four drugs are used as second line injectable drugs to treat drug resistant TB. Although these antibiotics belong to different class they have same mechanism of action of inhibiting the protein synthesis.

Kanamycin and amikacin inhibit the protein synthesis by binding to the 16s rRNA in the 30s ribosomal subunit.[65] Resistance to these antibiotics occurs mainly by mutations in rrs gene at positions 1400, 1401 and 1483. High level resistance occurs as a result of mutations at position 1400, 1401 and a mutation at 1484 confers low level resistance.[67] These rrs mutations are also associated with cross-resistance to other ribosomal binding drugs such as capreomycin and viomycin.[66]

Although full cross resistance between kanamycin and amikacin was previously assumed, few studies have shown the amikacin susceptibility in kanamycin resistant isolates, demonstrating highly variable levels and patterns of resistance suggesting that other mechanisms of resistance might be possible.[69] A recent study founded the mutations in the promoter region of the aminoglycoside acetyltransferase gene EIS (Rv2416c), this confers low level resistance to kanamycin but not amikacin. This mutation increases the expression of EIS gene and was found in 80% of clinical isolates showing low level resistance.[68]

Recent studies have found the mutations in the 5' untranslated region (UTR) of WhiB7, a transcriptional activator of EIS. This confers low level resistance by enhancing EIS expression.[72]

Capreomycin and viomycin have similar structure and bind at the same ribosomal site at the interface of two ribosomal sub units and inhibit protein synthesis. Mutations in the gene tlyA are associated with resistance to capreomycin and viomycin. TlyA codes for rRNA methyltransferase specific for 2'-o- methylation of ribose in rRNA.[70, 59, 71]

Ethionamide

Ethionamide is a congener of thioisonicotinamide and structurally similar to isoniazid. It is a prodrug and it is activated by the FAD-containing monooxygenase (encoded by ethA gene) to 2-ethyl 4-amino pyridine. This form adduct with NAD and inhibit the synthesis of mycolic acid by inhibiting enoyl-ACP reductase of fatty acid synthase-2 (encoded by inhA gene).[25] Production of ethA is regulated by transcriptional repressor ethR.[73]

Mutations in ethA, ethR or inhA confer resistance to ethionamide. Single amino acid mutation in inhA (S94A) confers co-resistance to isoniazid and ethambutol. This mutation leads to the over expression of inhA gene[74]. Studies with spontaneous isoniazid and ethionamide mutations of M.tuberculosis, map to mshA gene, encoding an enzyme essential for mycothiol biosynthesis as a target for ethionamide resistance. This study has also reported that mshA mutations confer co-resistance to isoniazid and ethambutol.[75]

Fluoroquinolones

Fluoroquinolones are the broad spectrum bactericidal antimicrobial agents and used as the second line agents in the treatment of MDR-TB. The older fluoroquinolones such as ciprofloxacin, olfoxacin are derivatives of nalidixic acid. New generation flouroquinoles such as levofloxacin, gatifloxacin, moxifloxacin is currently being considered for use in MDR-TB. Recent studies have shown that combination of fluoroquinolones, rifampin and pyrazinamide may shorten the duration of therapy needed to cure human TB.[77] The cellular target of fluoroqinolones in M. tuberculosis is DNA gyrase, a type 2 topoisomerase that controls negative supercoiling of DNA. Type 2 topoisomerase is a tetramer, consisting of two A and two B subunits that are encoded by gyrA and gyrB genes respectively. The important mechanism for the development of fluoroquinolone resistance is by missense mutations causing amino acid alterations in the quinolone resistant determining region (QRDR) of gyrA and gyrB. The fluoroquinolone resistant isolates more frequently contain mutations in the gyrA gene, particularly at codon 90, 94 and occasionally at codon 74, 88 and 91. Codon 95 contains a naturally occurring polymorphism (AGC, ser; or ACC, Thr) that may be unrelated to fluoroquinolone resistance because it occurred in both fluoroquinolones susceptible and resistant isolates.[80]

Few studies have reported the resistanc e to new generation drugs.[81] Although full cross- resistance is commonly assumed between fluoroquinolones, a recent study has shown that a strain with Asn-533-Thr mutation in gyrB is resistant to moxifloxacon and galtifloxacin but susceptible to ofloxacin.[82]

Several studies have reported the role of efflux mechanisms on resistance to fluoroquinolones. ATP-binding cassette (ABC) transporter have been described in M. tuberculosis. ABC transporters occupy 2.5% of genome but most of these ABC transporters have not been characterized.[83]

Subray S Hegde et al. described a fluoroquinolone resistant protein from M. tuberculosis. Expression of MfpA, a member of the pentapeptide repeat family of protein, causes resistance to ciprofloxacin and sparfloxacin, this protein binds to DNA gyrase and inhibits its activity.[84]

Para-amino salicylic acid

Para-amino salicylic acid is one of the oldest drugs to show anti TB activity. In combination with streptomycin and isoniazid, para -amino salicylic acid is used as a second line agent in treating TB. Para-amino salicylic acid is structural analogue of PABA, and competes with it for the enzyme dihydropteroate synthase, inhibiting folate synthesis.[25]

Resistance to p-amino salicylic acid is mediated by the mutations in thymidylate synthase gene (thyA). Studies have shown that only 37% of para- amino salicylic acid resistance isolates have mutations in thymidylate synthase A (thy A). This suggests the existence of additional mechanisms for p-amino salicylic acid resistance.[85]

A recent study has identified the mutations in FolC gene, encoding dihydro folate synthase, this confers resistance to para-amino salicylic acid.[86]

Cycloserine

Cycloserine is D-4-amino-3-isoxazolidone. It is a structural analogue of D-alanine and it is important second line agent used to treat MDR-TB. Cycloserine inhibits alanine racemase, which converts L-alanine to D-alanine and it also inhibits D-alanine: D-alanine ligase, thus blocking the formation of bacterial cell wall.[25]

A study by Caceres et al showed that overexpression of alrA led to the resistance to cycloserine in recombinant mutations.[86] Recent studies have shown that point mutations in cycA partially contribute to cycloserine resistance in
M. bovis BCG. CycA is a D-serine, L- and D-alanine and glycine transporter, it helps in uptake of cycloserine.[87]

NEW ANTI-TB DRUGS

Bedaquiline

Bedaquiline is approved by the FDA in 2012. It is in combination with other TB drugs to treat multi drug resistant TB (MDR-TB). Bedaquiline is a diarylquinoline; it acts by binding to subunit c of the ATP synthase of M. tuberculosis leading to inhibition of proton pump activity of the ATP aynthase.[25]

Resistant to bedaquiline is mainly mediated by the point mutations in its target atpE gene. Most frequently reported mutations are A63P and I66M; these mutations confer high level resistance, with up to 4 fold increase in MIC.[55] In a study by Huitric et al. gene sequencing of 53 invitro mutants revealed 5 single point mutations (A28V, A63P, I66M, A28P, G61A) within the atpE gene in only 15 isolates and no mutations were detected within atpE in other 38isolates, indicating other alternative resistance mechanisms.[88,93]

Non target based mutations, such as mutations in RV0678, a transcriptional repressor of the genes encoding the Mmps5-MmpL5 efflux pump, resulting in low level bedaquiline resistance and cross resistance to clofazimine.[89, 90] Recent studies have reported the mutations in the pepQ, encoding xaa-pro amino peptidase. This confers low level resistance to badaquiline and cross resistance to clofazimine. This mutation has reported to increase the MIC by 4times.[91, 92, 93]

Linezolid

Linezolid belongs to the class oxazolidiones. Oxazolidiones have been in clinical use for over a decade for the treatment of gram-positive cocci. Linezolid is the first antibiotic of this class to be approved for the treatment of MDR-TB.[25] Linezolid acts by inhibiting the early steps of protein synthesis by binding to the 50s subunit of ribosomes. Linezolid has high invitro and invivo activity against M. tuberculosis. PNU100480 a structural analogue of linezolid showed similar activity like rifampicin and isoniazid in various combinations.[94]

Resistance to linezolid in M. tuberculosis has been associated with the mutation in the 23s rRNA (rrl) gene. Richard et al. in his study on 210 isolates of MDR-TB reported the linezolid resistance in 1.9% of isolates and no mutations were found in the target gene. MIC of resistant isolates ranged between 4-8 mg/l.[95] In a study by Hillemann on 10 linezolid resistant colonies reported mutations in G2061T and G2572T in rrl gene in 5 colonies and these mutations were associated with high level resistance with MIC range of 16-32mg/l. Remaining isolates showed no resistance in rrl gene and their MIC was 4-8 mg/l.[96]

More recent studies using next generation sequencing showed the mutation T460C in rplC gene, encoding the 50s ribosomal L3 protein in linezolid resistant isolates.[97]

Bicyclic nitroimidazoles: delamide and pretomanid

Pretomanid and delaminid are bicyclic nitroimidazopyrans that are being used in the treatment of XDR and MDR-TB. Pretomanid (previously called as PA-824) is a prodrug that requires activation by the bacteria via a nitroreduction step that requires a specific G6PDX, FGD1 and the reduced deazoflavin cofactor F420 encoded by RV 3547. The resulting active metabolite acts by 2 mechanisms; first under aerobic conditions it inhibits M. tuberculosis mycolic acid and protein synthesis. Second in non-replicating persistent bacilli (NRPB) it generates reactive nitrogen species such as NO via its des-nitro metabolite, which then augment the kill of intracellular NRPB by innate immune system.[25,98] Delamanid is also a prodrug that is activated by the same enzyme encoded by RV 3547. Similarly it forms a reactive intermediate metabolite that inhibits mycolic acid production.[25,99]

Resistant to PA-824 is most commonly mediated by loss of specific glucose-6-phosphate dehydrogenase (FGD 1) or its deazaflavin cofactor F420.[100] In experimentally generated delamanid resistant mycobactera a mutation was found in the RV3547 gene, this suggests its role in the activation of drug.[101] Bloemerg et al. recently reported mutations in the fbiA and fgd1 genes that corresponded with increasing phenotypic delamanid resistance.[102]

Strategies for prevention and control of drug resistant TB

Indian government has launched program called India national strategic plan (NSP) for TB 2017-2025 with the aim of eradicating the TB and to make India a TB free with zero deaths.[104]

Center for disease control and prevention (CDC) is working with Indian government to control the drug resistant TB by[103]

1. By improving access to better screening, contact tracing and diagnostic tools to find TB cases.
2. Evaluating better TB treatment regimens and improving access to care and treatment.
3. Breaking the cycle of transmission by strengthening TB infection control, identifying hotspots to target screening efforts and scaling up treatment to prevent TB among vulnerable population.

The five principal ways to prevent drug resistant TB[105]

1. *Early detection and high-quality treatment of drug susceptible TB:* many people have undetected TB for too long. Late detection of TB increases the risk of transmission the disease to others. Early detection can be possible by creating awareness among public. Improving access and utilizing of high-quality TB services established across the health system, including private sector.[106]
   Identify the patients who require TB test. All the diagnosed patients should also be tested for the drug susceptibility and the susceptible patients should be effectively treated with treatment follow up. Care givers and clinical pharmacists should provide counseling to the patients regarding drug adherence. In every health care settings specific challenges for treatment adherence should be assessed and then appropriate mechanisms should be put in place to mitigate the consequences.
2. *Early detection and high-quality treatment of drug resistant TB:* early detection of drug resistant TB can be done by drug susceptibility testing (DST). In many low- and middle-income countries DST is done only in a fraction of all cases. This leads to a large number of undetectable drug resistant TB cases or severely delayed diagnosis of the majority of drug resistant TB cases.
3. *Infectious control:* these are taken to minimize the risk of TB transmission within populations. Infectious control policies should be well formulated and implemented at every level of health delivery, in homeless shelters, prisons, health care settings, refugee camps and at the household level.
4. *Health system strengthening and regulation:* health care system strengthening includes the improving of human resource development, diagnostic capacity and drug management with other public health programs. Health care system barriers should be identified and national TB control programs should be designed. WHO has provided guidelines for NTPs on how they can contribute to general health

system strengthening? TB programs can contribute to the hospital system strengthening through investments in laboratory infrastructure, capacity building of health staff and increased routine use of health data as well as by developing innovative service delivery strategies in response to specific health system barrier, such strategies include practical approach to lung health (PAL), public private mix (PPM) approaches and community-based care. These programs should regulate the availability of both first line and second line TB medicines and restrict use to those facilities where quality of prescription and treatment management can be ensured, in particular, banning over the counter sales of TB medicines should be strictly enforced.[105, 107]

5. *Addressing underlying risk factors and social determinants:* the most critical and immediate social intervention for prevention of drug resistant TB is to access and adherence to health care services and to address them accordingly. This includes providing all TB diagnostic and treatment services free of charge to patients for other clinical related services (such as comorbidities), as well as minimizing the indirect costs of care (those related to transport and loss of income). Access to available social protection schemes, including sickness/disability funds and other cash transfers, should be ensured for people with TB.

CONCLUSION

Tuberculosis is a contagious disease with various parameters for community spread involved in it. The question of improving the public health outcomes can be addressed with change in policies and protocols. The current article studies the various etiological parameters and various strategies to improve outcomes. Various types of epidemiological research need to be carried out in distant populations to intervene different sources in the structure and to understand the parameters completely.

Acknowledgement: NIL.
Conflict of Interest: NIL.
Source of Funding: NIL.

REFERENCES

1. https://www.cdc.gov/tb/topic/basics/default.htm.
2. https://www.who.int/activities/tackling-the-drug-resistant-tb-crisis.
3. https://www.who.int/tb/areas-of-work/drug-resistant-tb/types/en/.
4. dipiro 11 edition.
5. who-global tb report 2020.
6. Report of the first national anti-tuberculosis drug resistance survey India, 2014-16.
7. Chadha VK, Anjinappa SM, Dave P, Rade K, Baskaran D, et al. (2019) Sub-national TB prevalence surveys in India, 2006-2012: Results of uniformly conducted data analysis. Plos one, 14(2).
8. applied therapeutics 11 edition.
9. Seung KJ, Keshavjee S, Rich ML. Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. Cold Spring Harb Perspect Med, 2015.27; 5(9).
10. Seung KJ, Gelmanova IE, Peremitin GG, Golubchikova VT, Pavlova VE, Sirotkina OB, Yanova GV, Strelis AK. The effect of initial drug resistance on treatment response and acquired drug resistance during standardized short-course chemotherapy for tuberculosis. Clin Infect Dis, 2004; 39(9).
11. Lin H, Shin S, Blaya JA, Zhang Z, Cegielski P, Contreras C, Asencios L, Bonilla C, Bayona J, Paciorek CJ, Cohen T. Assessing spatiotemporal patterns of multidrug-resistant and drug-sensitive tuberculosis in a South American setting. Epidemiol Infect, 2011 Nov; 139(11): 1784-93.
12. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, Atwood S, Murray M. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bull World Health Organ, 2007 Sep; 85(9): 703-11.
13. https://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/areas-of-work/vulnerable-populations-risk-factors-and-social-determinants/tb-in-prisons.
14. https://www.who.int/tb/areas-of-work/population-groups/prisons-facts/en/.
15. Droznin M, Johnson A, Johnson AM. Multidrug resistant tuberculosis in prisons located in former Soviet countries: A systematic review. PLoS One, 2017 Mar 23; 12(3).
16. Biadglegne F, Rodloff AC, Sack U. Review of the prevalence and drug resistance of tuberculosis in prisons: a hidden epidemic. Epidemiol Infect, 2015 Apr; 143(5): 887-900.
17. Michael JS, John TJ. Extensively drug-resistant tuberculosis in India: a review. Indian J Med Res, 2012 Oct; 136(4): 599-604.
18. Saktiawati AMI, Subronto YW. Influence of Diabetes Mellitus on the Development of Multi Drug Resistant-Tuberculosis in Yogyakarta. Acta Med Indones, 2018 Jan; 50(1): 11-17.
19. Chang JT, Dou HY, Yen CL, Wu YH, Huang RM, Lin HJ, Su IJ, Shieh CC. Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: a potential role in the emergence of multidrug-resistance. J Formos Med Assoc, 2011 Jun; 110(6): 372-81.
20. Saldanha N, Runwal K, Ghanekar C, Gaikwad S, Sane S, Pujari S. High prevalence of multi drug resistant tuberculosis in people living with HIV in Western India. BMC Infect Dis, 2019 May 8; 19(1): 391.

21. Sachin R Atre, Desiree T.B. D'Souza, Tina S Vira, Anirvan Chatterjee, Nerges F Mistry. Risk factors associated with MDR-TB at the onset of therapy among new cases registered with the RNTCP in Mumbai, India. Indian journal of public health, 2011; 55(1): 14-21.
22. Helen Suzanne Cox, Tanja Kubica, Daribay Doshetov, Yared Kebede, Sabine Rusch-Gerdess, Stefan Niemann. The Beijing genotype and drug resistant tuberculosis in the Aral Sea region of central Asia. Respiratory research, 2005; 6(1): 134.
23. O. Narvkaya, T. Otten, E. Limeschenko, N. Sapozhnikova, O. Graschenkova et al. c European Journal of Clinical Microbiology and Infectious Diseases, 2014; 21(8): 596-602.
24. Elizabeth Clara Barroso, Rosa Maria Salani Mota, Raimunda Oliveira Santos, Ana Lúcia Oliveira Sousa et al. Risk factors for acquired multidrug-resistant tuberculosis. Jornal de pneumologia, 2003; 29(2).
25. Laurence L Brunton; The Pharmacological Basis of Therapeutics, 13th Edition, Section 7, Chapter 60 "Page: 1067-1086".
26. Akos Somoskovi, Linda M Parsons and Max Salfinger. The molecular basis of resistance to isoniazid, rifampin and pyrazinamide in mycobacterium tuberculosis. Respiratory Research, 2001; 2(3): 164-168.
27. Navisha Dookie, Santhuri Rambaran, Nesri Padayatchi, Sharana Mahomed, Kogieleum Naidoo. Evolution of drug resistance in mycobacterium tuberculosis: a review on the molecular determinants of resistance and implications for personalized care. Journal of Antimicrobial chemotherapy, 2018; 73(5): 1138-1151.
28. Diana Machado, Joao Perdigao, Jorge Ramos, Isabel Couto, Isabel Portugal et al. High-level resistance to isoniazid and ethionamide in multidrug-resistant Mycobacterium tuberculosis of the Lisboa family is associated with InhA double mutations. Journal of Antimicrobial Chemotherapy, 2013; 68(8): 1728-1732.
29. Yu Min Ho, Yong-Jiang Sun, Sin-Yew Wong, Ann S.G Lee. Contribution of dfrA and InhA mutations to the detection of isoniazid-Resistant Mycobacterium tuberculosis isolates. Antimicrobial Agents and Chemotherapy
30. Michelle H. Larsen, Catherine Vilcheze, Laurent kremer, Gurdyal S. Besra, Linda Parsons et al. overexpression of InhA, but not KasA, confers resistance to isonoazid and ethionamide in Mycobacterium smegmatis, M. bovis BCG and M. tuberculosis. Molecular microbiology, 2002; 46(2): 453-466.
31. H. Rinder, A. Thomschke, S. Rusch-Gerdes, G. Bretzel, K.Feldmann, M. Rifai et al. Significance of ahpC promoter mutations for the prediction of isoniazid resistance in Mycobacterium tuberculosis. European journal of Clinical Microbiology and Infectious Diseases, 1998; 17: 508-511.
32. H J Marttila, H Soini, E Eerola, E Vyshnevskaya et al. A Ser315thr substitution in KatG is predominant in genetically heterogeneous multidrug-resistant Mycobacterium tuberculosis isolates originating from the St. Petersburg area in Russia. Antimicrobial agents and chemotherapy, 1998; 42(9): 2443-5.
33. Hiroki Ando, Tomoe Kitao, Tohru Miyoshi-Akiyama, Seiya Kato, Toru Mori, Teruo Kirikae. Downregulation of KatG expression is associated with isoniazid resistance in Mycobacterium tuberculosis. Molecular microbiology, 2011; 79(6): 1615-1628.
34. S Sreevatsan, X Pan, Y Zhang, V Deretic, J M Musser. Analysis of the OxyR-ahpC region in isoniazid-resistant-susceptible Mycobacterium tuberculosis complex organisms recovered from diseased humans and animals in diverse localities. American society for microbiology, 1997; 41(3): 600-606.
35. Elis R Dalla Costa, Marta O ribeiro, Marcia SN Silva, Liane S Arnold, Diana C Rostrolla et al. correlations of mutations in KatG, oxyR-ahpC and inhA genesand invitro susceptibility in mycobacterium tuberculosis clinical strains segregated by spoligotype families from tuberculosis prevalent countries in south America. BMC microbiology, 2009; 9(39).
36. Pedro Eduardo Almeida Da Ailva, Juan Carlos Palomino. Molecular basics and mechanisms of drug resistance in mycobacterium tuberculosis: classical and new drugs. Journal of antimicrobial chemotherapy, 2011; 66(7): 1417-1430.
37. D.A. Mitchison, A.J. Nunn. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. ATS journal, 1985; 133(3).
38. Glenn P. Morlock, Bonnie B. Plikaytis, Jack T. Crawford. Characterization of spontaneous, In Vitro-selected, rifampin-resistant mutations of Mycobacterium tuberculosis strain H37Rv: Antimicrobial agents and chemotherapy. American society for microbiology, 2000.
39. Berhe G, Enqueselassie F, Hailu E, Mekonnen W, Teklu T, Gebretsadik A, Berhe R, Haile T, Aseffa A. Population-based prevalence survey of tuberculosis in the Tigray region of Ethiopia. BMC Infect Dis, 2013 Sep 28; 13: 448.
40. M Caws, Phan Minh Duy, Dau Quang Tho, Nguyen Thi Ngoc Lan, Dai Viet Hoa et al. mutations prevalent among rifampin and isoniazid resistant Mycobacterium tuberculosis isolates from a hospital in Vietnam: journal of clinical Microbiology. American society for microbiology, 2006; 44(7): 2333-2337.
41. S L Moghazeh, X Pan, T Arain, C K Stover, J M Musser and B N kreiswirth. Comparative antimycobacterial activities of rifampin, rifapentine and KRM-1648 against a collection of rifampin-resistanct Mycobacterium tuberculosis isolates with

known rpoB mutations: Antimicrobial agents and chemotherapy. American society for microbiology, 1996; 40(11): 2655-2657.
42. H Ohno, H Koga, S Kohno, T Tashiro, K Hara. Relationship between rifampin MICs for and ropB mutations of mycobacterium tuberculosis strains isolated in Japan: Antimicrobial agents and chemotherapy. American society for microbiology, 1996; 40(4): 1053-1056.
43. Inaki comas, Sonia Borrell, Andreas Roetzer, Graham Rose et al. Whole-genome sequencing of rifampicin-resistant M. tuberculosis strainidentifyes compensatory mutations in RNA polymerase. Nature genetics, 2012; 44(1): 106-110.
44. M.de vos, B.Mullar, s.Borrell, et al. Putative compensatory mutations in the rpoc gene of rifampin resistant mycobacterium tuberculosis are associated with ongoing transmission. Antimicrobial agents and chemotherapy, 2012; 57: 827-832.
45. H.Traore, K.Fissette, I.Bastian, et al. Detection of rifampicin resistance in mycobacterium tuberculosis isolates from diverse countries by a commercial line probe assay as an initial indicator of multidrug resistance. The international journal of tuberculosis and lung disease, 1999; 481-484.
46. L.Heifets, P Lindholm-levy. American review of respiratory disease: pyrazinamide sterilizing activity in-vivo against semi dormant mycobacterium tuberculosi bacterial population. ATS journals, 1992; 145(5): 1223-5.
47. Ying Zhang, Wanliang Shi, Wenhong Zhang, and Denis Mitchison. Mechanism of pyrazinamide action and resistance. Microbiology spectrum, 2014.
48. Michael G.Whitfield, Heidi M.Soeters, Talita York, et al. A global perspective on pyrazinamide resistance: systemic review and mata analysis, 2015.
49. K Hirano, M Takhashi, Y kazumi, Y Fukasawa, C Abe. Mutation in pncA is a major mechanism of pyrazinamide resistance in mycobacterium tuberculosis. Tuber Lung Dis, 1997; 78(2): 117-22.
50. Wanliang shi, Xuelian Zhang, Xin Jiang, Haiming Yuan, et al. Pyrazinamide inhibits trans-translation in mycobacterium tuberculosis. Science, 201; 333: 1630-1632.
51. Jim Werngren, Erik Alm, Mikael Mansjo. Non – pncA gene-mutated but pyrazinamide-resistant mycobacterium tuberculosis: why is that? Journal of clinical microbiology, 2017; 55.
52. Matteo Zignol, Anna S Dean, Sonke Andres, et al. Population based resistance of mycobacterium tuberculosis isolates of pyrazinamide and fluroquinolones: results from a multi country surveillance project. The lancet infectious diseases, 2016; 16: pages 1185-1192.
53. Srinand sreevatsan, Kathryn E stockbauer, Xi pan, Barry N.Kreiswirth, Soraya L, Moghazeh et al. Ethambutol resistance in mycobacterium tuberculosis: critical role of embB mutations. Antimicrobial agents and chemotherapy, 2997; 41(8): 1677-1681.
54. Manzour Hernando Hazbón, Miriam Bobadilla del Valle, Marta Inírida Guerrero, Mandira Varma-Basil, Ingrid Filliol, Magali Cavatore, et al. Role of embB Codon 306 Mutations in Mycobacterium tuberculosis Revisited: a Novel Association with Broad Drug Resistance and IS6110 Clustering Rather than Ethambutol Resistance: antimicrobial agents and chemotherapy. American society for microbiology, 2005; 49(9): 3794-3802.
55. Petrella S, Cambau E, Chauffour A, Andries K, Jarlier V, Sougakoff W. Genetic basis for natural and acquired resistance to the diarylquinoline R207910 in mycobacteria. Antimicrob Agents Chemother, 2006 Aug; 50(8): 2853-6.
56. Ann S. G. Lee, Siti Noor Khadijah Othman, Yu Min Ho, Sin Yew Wong. Novel Mutations within the embB Gene in Ethambutol-Susceptible Clinical Isolates of Mycobacterium tuberculosis: Antimicrobial agents and chemotherapy. American society for microbiology, 2004; 48(11): 4447-4449.
57. Claudia Plinke , Helen S Cox, Nana Zarkua, Hamraev A Karimovich, Kai Braker, Roland Diel, Sabine Rüsch-Gerdes, Silke Feuerriegel, Stefan Niemann. EmbCAB sequence variation among ethambutol-resistant Mycobacterium tuberculosis isolates without embB306 mutation. Journal of antimicrobial chemotherapy, 2010; 65(7): 1357-1367.
58. Hassan Safi, Subramanya Lingaraju, Anita Amin, Soyeon Kim, Marcus Jones, Michael Holmes, Evolution of high-level ethambutol-resistant tuberculosis through interacting mutations in decaprenylphosphoryl-β-D-arabinose biosynthetic and utilization pathway genes. Natural genesis, 2013; 45: 1190-1197.
59. Juan Carlos palomino, Anandi Martin. Drug resistance mechanism in mycobacterium tuberculosis. Antibiotics, 2014; 3(3): 317-340.
60. Danesh Moazed and Harry F. Noller. Interaction of antibiotics with functional sites in 16s ribosomal RNA. Nature, 1987; 327: 389-394.
61. Marion Finken, Philip Kirschner, Albrecht Meier, Annette Wrede, Erik C. Böttger. Molecular basis of streptomycin resistance in Mycobacterium tuberculosis: alterations of the ribosomal protein S12 gene and point mutations within a functional 16S ribosomal RNA pseudoknot. Molecular microbiology, 1993; 9(6): 1239-1246.
62. S Sreevatsan [1], X Pan, K E Stockbauer, D L Williams, B N Kreiswirth, J M MusserCharacterization of rpsL and rrs mutations in streptomycin-resistant Mycobacterium tuberculosis isolates from diverse geographic localities: Antimicrobial agents and chemotherapy. American society for microbiology, 1996; 40(4): 1024-1026.
63. Fei Zhao, Xu-De Wang, Luke N. Erber, Ming Luo, Ai-zhen Guo, Shan-Shan Yang, Jing Gu, Binding Pocket Alterations in Dihydrofolate Synthase Confer Resistance to para-Aminosalicylic Acid in Clinical Isolates of Mycobacterium tuberculosis.

Antimicrobial agents and chemotherapy. American society for microbiology, 2014; 58(3): 1479-1487.
64. Susumu Okamoto Aki Tamaru Chie Nakajima Kenji Nishimura Yukinori Tanaka Shinji Tokuyama Yasuhiko SuzukiKozo Ochi Loss of a conserved 7-methylguanosine modification in 16S rRNA confers low-level streptomycin resistance in bacteria. Molecular microbiology, 2007; 63(4): 1096-1106.
65. Freerksen E, Orlowski E-H, Thumin H-J (eds): Experimental and Clinical Evaluation of the Tuberculostatics Capreomycin, Isoxyl, Myambutok, Rifampicin. International Colloquium, Borstel, Antibiot Chemother. Basel, Karger, 1970; 16: 369-379.
66. Levan Jugheli, Nino Bzekalava, Pim de Rijk, Krista Fissette, Françoise Portaels, Leen Rigouts. High Level of Cross-Resistance between Kanamycin, Amikacin, and Capreomycin among Mycobacterium tuberculosis Isolates from Georgia and a Close Relation with Mutations in the rrs Gene. Antimicrobial agents and chemotherapy: American society for microbiology, 2009; 53(12): 5064-5068.
67. Feuerriegel S, Cox HS, Zarkua N, Karimovich HA, Braker K, Rüsch-Gerdes S, Niemann S. Sequence analyses of just four genes to detect extensively drug-resistant Mycobacterium tuberculosis strains in multidrug-resistant tuberculosis patients undergoing treatment. Antimicrob Agents Chemother, 2009 Aug; 53(8): 3353-6.
68. M. Analise Zaunbrecher, R. David Sikes Jr., Beverly Metchock, Thomas M. Shinnick, and James E. Posey. Overexpression of the chromosomally encoded aminoglycoside acetyltransferase eis confers kanamycin resistance in Mycobacterium tuberculosis.Proceedings of the National Academy of Sciences, 2009; 106(47): 20004-20009.
69. Krüüner, A., Jureen, P., Levina, K., Ghebremichael, S., & Hoffner, S. (2003). Discordant resistance to kanamycin and amikacin in drug-resistant Mycobacterium tuberculosis. Antimicrobial agents and chemotherapy, 47(9): 2971–2973.
70. Shanna K. Johansen, Courtney E. Maus, Bonnie B. Plikaytis, Stephen Douthwaite. Capreomycin binds across the Ribosomal Subunit Interface Using tlyA-Encoded 2′-O-Methylations in 16S and 23S rRNAs. Molecular cell, 2006; 23(2): 173-182.
71. Maus CE, Plikaytis BB, Shinnick TM. Mutation of tlyA confers capreomycin resistance in Mycobacterium tuberculosis. Antimicrob Agents Chemother, 2005; 49(2): 571-7.
72. Rowan P. Morris, Liem Nguyen, John Gatfield, Kevin Visconti, Kien Nguyen, Dirk Schnappinger, Sabine Ehrt, Ancestral antibiotic resistance in Mycobacterium tuberculosis.Proceedings of the National Academy of Sciences, 2005; 102(34): 12200-12205.
73. Carette X, Blondiaux N, Willery E, Hoos S, Lecat-Guillet N, Lens Z, Wohlkönig A, Wintjens R, Soror SH, Frénois F, Dirié B, Villeret V, England P, Lippens G, Deprez B, Locht C, Willand N, Baulard AR. Structural activation of the transcriptional repressor EthR from Mycobacterium tuberculosis by single amino acid change mimicking natural and synthetic ligands. Nucleic Acids Res, 2012 Apr; 40(7): 3018-30.
74. Vilchèze C, Jacobs WR Jr. Resistance to Isoniazid and Ethionamide in Mycobacterium tuberculosis: Genes, Mutations, and Causalities. Microbiol Spectr, 2014 Aug; 2(4).
75. Catherine Vilchèze Yossef Av-Gay Rodgoun Attarian Zhen Liu, Manzour H. Hazbón Roberto Colangeli et al. Mycothiol biosynthesis is essential for ethionamide susceptibility in Mycobacterium tuberculosis. Molecular microbiology, 2008; 69(5): 1316-1329.
76. Alvirez-Freites EJ, Carter JL, Cynamon MH. In vitro and in vivo activities of gatifloxacin against Mycobacterium tuberculosis. Antimicrob Agents Chemother, 2002; 46(4): 1022-5.
77. Nuermberger EL, Yoshimatsu T, Tyagi S, Williams K, Rosenthal I, O'Brien RJ, Vernon AA, Chaisson RE, Bishai WR, Grosset JH. Moxifloxacin-containing regimens of reduced duration produce a stable cure in murine tuberculosis. Am J Respir Crit Care Med, 2004; 170(10): 1131-4.
78. Suhail Ahmad, Eiman Mokaddas. Role of fluoroquinolones in the treatment of tuberculosis. Review in health care, 2012; 3(1): 17-31.
79. Aubry A, Veziris N, Cambau E, Truffot-Pernot C, Jarlier V, Fisher LM. Novel gyrase mutations in quinolone-resistant and -hypersusceptible clinical isolates of Mycobacterium tuberculosis: functional analysis of mutant enzymes. Antimicrob Agents Chemother, 2006 Jan; 50(1): 104-12. Doi:10.1128/AAC.50.1.104-112.2006. PMID:16377674; PMCID:PMC1346799.
80. Musser JM. Antimicrobial agent resistance in mycobacteria: molecular genetics insights. Clin Microbiol Rev, 1995 Oct; 8(4): 496-514. doi:10.1128/CMR.8.4.496-514.1995. PMID:8665467; PMCID: PMC172873.
81. El Sahly HM, Teeter LD, Jost KC Jr, Dunbar D, Lew J, Graviss EA. Incidence of moxifloxacin resistance in clinical Mycobacterium tuberculosis isolates in Houston, Texas. J Clin Microbiol, 2011; 49(8): 2942-2945.
82. Andrea Von Groll, Anandi Martin, Pontus Jureen, Sven Hoffner, Peter Vandamme, et al. Fluoroquinolone Resistance in Mycobacterium tuberculosis and Mutations in gyrA and gyrB. Antimicrob Agents Chemother. 2009; 53(10): 4498-4500.
83. Choudhuri BS, Bhakta S, Barik R, Basu J, Kundu M, Chakrabarti P. Overexpression and functional characterization of an ABC (ATP-binding cassette) transporter encoded by the genes drrA and drrB of Mycobacterium tuberculosis. Biochem J. 2002 Oct

1; 367(Pt 1): 279-85. doi:10.1042/BJ20020615. PMID: 12057006; PMCID: PMC1222852.
84. Hegde SS, Vetting MW, Roderick SL, Mitchenall LA, Maxwell A, Takiff HE, Blanchard JS. A fluoroquinolone resistance protein from Mycobacterium tuberculosis that mimics DNA. Science, 2005 Jun 3; 308(5727): 1480-3. doi:10.1126/science.1110699. PMID:15933203.
85. Vanessa Mathys, René Wintjens, Philippe Lefevre, Julie Bertout, Amit Singhal, Mehdi Kiass. Molecular Genetics of para-Aminosalicylic Acid Resistance in Clinical Isolates and Spontaneous Mutants of Mycobacterium tuberculosis. Antimicrob Agents Chemother, 2009; 53(5): 2100-2109.
86. Cáceres NE, Harris NB, Wellehan JF, Feng Z, Kapur V, Barletta RG. Overexpression of the D-alanine racemase gene confers resistance to D-cycloserine in Mycobacterium smegmatis. J Bacteriol, 1997 Aug; 179(16): 5046-55.
87. Chen JM, Uplekar S, Gordon SV, Cole ST. A point mutation in cycA partially contributes to the D-cycloserine resistance trait of Mycobacterium bovis BCG vaccine strains. PLoS One, 2012; 7(8): e43467.
88. Huitric E, Verhasselt P, Koul A, Andries K, Hoffner S, Andersson DI. Rates and mechanisms of resistance development in Mycobacterium tuberculosis to a novel diarylquinoline ATP synthase inhibitor. Antimicrob Agents Chemother, 2010 Mar; 54(3): 1022-8.
89. Andries K, Villellas C, Coeck N, Thys K, Gevers T, Vranckx L, et al. (2014) Acquired Resistance of Mycobacterium tuberculosis to Bedaquiline. PLoS ONE, 9(7): e102135.
90. Hartkoorn RC, Uplekar S, Cole ST. Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in Mycobacterium tuberculosis. Antimicrob Agents Chemother, 2014 May; 58(5): 2979-81. doi:10.1128/AAC.00037-14. Epub 2014 Mar 3. PMID: 24590481; PMCID: PMC3993252.
91. Almeida D, Ioerger T, Tyagi S, Li SY, Mdluli K, Andries K, Grosset J, Sacchettini J, Nuermberger E. Mutations in pepQ Confer Low-Level Resistance to Bedaquiline and Clofazimine in Mycobacterium tuberculosis. Antimicrob Agents Chemother, 2016 Jul 22; 60(8): 4590-9. doi:10.1128/AAC.00753-16. PMID:27185800; PMCID:PMC4958187.
92. Ghajavand H, Kargarpour Kamakoli M, Khanipour S, Pourazar Dizaji S, Masoumi M, Rahimi Jamnani F, Fateh A, Siadat SD, Vaziri F. High Prevalence of Bedaquiline Resistance in Treatment-Naive Tuberculosis Patients and Verapamil Effectiveness. Antimicrob Agents Chemother, 2019 Feb 26; 63(3): e02530-18. doi:10.1128/AAC.02530-18. PMID:30602521; PMCID: PMC6395892.
93. Nguyen TVA, Anthony RM, Bañuls AL, Nguyen TVA, Vu DH, Alffenaar JC. Bedaquiline Resistance: Its Emergence, Mechanism, and Prevention. Clin Infect Dis, 2018 May 2; 66(10): 1625-1630. doi:10.1093/cid/cix992. PMID: 29126225.
94. Cynamon MH, Klemens SP, Sharpe CA, Chase S. Activities of several novel oxazolidinones against Mycobacterium tuberculosis in a murine model. Antimicrob Agents Chemother, 1999 May; 43(5): 1189-91. doi:10.1128/AAC.43.5.1189. PMID: 10223934; PMCID:PMC89131.
95. Richter E, Rüsch-Gerdes S, Hillemann D. First linezolid-resistant clinical isolates of Mycobacterium tuberculosis. Antimicrob Agents Chemother, 2007 Apr; 51(4): 1534-6. doi:10.1128/AAC.01113-06. Epub 2007 Jan 22. PMID: 17242139; PMCID: PMC1855508.
96. Hillemann D, Rüsch-Gerdes S, Richter E. In vitro-selected linezolid-resistant Mycobacterium tuberculosis mutants. Antimicrob Agents Chemother, 2008 Feb; 52(2): 800-1. doi:10.1128/AAC.01189-07. Epub 2007 Dec 10. PMID: 18070973; PMCID: PMC2224755.
97. Beckert P, Hillemann D, Kohl TA, Kalinowski J, Richter E, Niemann S, Feuerriegel S. rplC T460C identified as a dominant mutation in linezolid-resistant Mycobacterium tuberculosis strains. Antimicrob Agents Chemother, 2012 May; 56(5): 2743-5. doi:10.1128/AAC.06227-11.Epub 2012 Feb 27. PMID:22371899; PMCID: PMC3346602.
98. Bashiri G, Squire CJ, Moreland NJ, Baker EN. Crystal structures of F420-dependent glucose-6-phosphate dehydrogenase FGD1 involved in the activation of the anti-tuberculosis drug candidate PA-824 reveal the basis of coenzyme and substrate binding. J Biol Chem, 2008 Jun 20; 283(25): 17531-41. doi:10.1074/jbc.M801854200. Epub 2008 Apr 22. PMID: 18434308.
99. Xavier AS, Lakshmanan M. Delamanid: A new armor in combating drug-resistant tuberculosis. J Pharmacol Pharmacother, 2014 Jul; 5(3): 222-4. doi:10.4103/0976-500X.136121. PMID: 25210407; PMCID: PMC4156838.
100. Manjunatha UH, Boshoff H, Dowd CS, Zhang L, Albert TJ, Norton JE, Daniels L, Dick T, Pang SS, Barry CE 3rd. Identification of a nitroimidazo-oxazine-specific protein involved in PA-824 resistance in Mycobacterium tuberculosis. Proc Natl Acad Sci U S A, 2006 Jan 10; 103(2): 431-6. doi:10.1073/pnas.0508392103. Epub 2005 Dec 30. PMID: 16387854; PMCID: PMC1326169.
101. Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, Shimokawa Y, Komatsu M. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med, 2006 Nov; 3(11): e466. doi:10.1371/journal.pmed.0030466. PMID: 17132069; PMCID: PMC1664607.
102. Bloemberg GV, Keller PM, Stucki D, Trauner A, Borrell S, Latshang T, Coscolla M, Rothe T, Hömke R, Ritter C, Feldmann J, Schulthess B, Gagneux S, Böttger EC. Acquired Resistance to Bedaquiline and

Delamanid in Therapy for Tuberculosis. N Engl J Med, 2015 Nov 12; 373(20): 1986-8. doi:10.1056/NEJMc1505196. Erratum in: N Engl J Med, 2015 Dec 17; 373(25): e29. Stuckia, David [corrected to Stucki, David]. PMID: 26559594; PMCID: PMC4681277.

103. https://www.cdc.gov/drugresistance/solutions-initiative/stories/mdrtb-in-india.html
104. https://tbfacts.org/tb-india-plan/#:~:text=The%20Goal%20is%20to%20achieve,TB%20in%20India%20by%202025.&text=Detect%2C%20Treat%2C%20Prevent%20%26%20Build,is%20that%20of%20Key%20Populations.
105. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2014. 1, Prevention of drug-resistant tuberculosis.
106. https://www.ncbi.nlm.nih.gov/books/NBK247443/
107. https://apps.who.int/iris/bitstream/handle/10665/43978/9789241597173_eng.pdf;jsessionid=7F02CA3142C38768B311169A219FAAB9?sequence=1