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Recent Advancement of Tubercular Therapy in MDR-TB and DR-TB

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Abstract: ***Despite international efforts to control and eradicate tuberculosis (TB), it continues to be a major cause of morbidity and mortality on a global scale. Drug-resistant TB (DRTB) is a serious public health threat that affects global health security, economic burden, and access to high-quality care. To effectively address this issue, cooperation between governments, international organizations, and healthcare systems is essential. In December 2012, the Food and Drug Administration (FDA) granted accelerated approval for bedaquiline (BDQ), a diarylquinoline drug, based on analysis of time to sputum culture conversion from two phase 2 trials.Although drug resistance is an inevitable side effect of drug use, multi-drug resistance can be controlled with precise diagnosis and customized treatment plans.Mycobacterium in MDR-TB is resistant to frontline medications such as isoniazid and rifampicin. Over 50% of medications are now resistant, making identification and treatment a pressing worldwide concern.More than any other infectious disease, tuberculosis (TB) ranks as the ninth leading cause of mortality worldwide. Due to increasing drug resistance, the epidemic is still present and will need substantial attention and funding to be eradicated. Despite the relatively low number of resources committed, several significant advancements have recently been made through increased collaboration and research networks. Drug-resistant TB regimens are increasingly using the newly available medications bedaquiline and delamanid as well as the repurposed medications linezolid, clofazimine, and carbapenems.In addition to appropriate use and drug resistance monitoring, combination therapy with additional anti-TB medications is recommended to prevent resistance. Following positive results from a phase III trial, the US FDA approved Pretomanid in August 2019. Pretomanid, linezolid, bedaquiline, A part of the BPaLM regimen, and moxifloxacin, has been authorized for the treatment of individuals with treatment-intolerant or non-responsive MDRTB or extensive pulmonary DRTB. Patients with MDRTB now have better clinical results and a higher quality of life because to this important management breakthrough. The WHO guidelines' inclusion is positive for the worldwide fight against DRTB. New therapeutic targets within the TB pathogenesis have been found and studied by researchers, providing encouraging opportunities for the creation of novel anti-TB medications.***

Keywords: Tuberculosis; Multidrug-resistance Tuberculosis, Drug-resistance Tuberculosis, New Drugs;Bedaquiline, Pretomanid , Linezolid and Moxifloxacin Regimen

I. INTRODUCTION

Globally, tuberculosis (TB) is the biggest cause of death from a single infectious agent, despite being an infectious illness that can be both prevented and successfully treated. Only 186 772 of the approximately half a million new cases of rifampicin-resistant TB (RR-TB) in 2018 were diagnosed, and even fewer began receiving the proper treatment. These cases included multidrug-resistant TB and multidrug-resistant tuberculosis (MDR-TB), which is resistance to both rifampicin and isoniazid.[1] Out of the 156 071 individuals who were enrolled in treatment, only 56% received successful treatment; this percentage hasn't improved much in decades.[1]The WHO first suggested the new medication bedaquiline (Bdq) for the treatment of certain types of Adults with RR/MDR-TB in June 2013.[2]. The WHO suggested delamanid (Dlm), a second novel antituberculosis medication, in October 2014 to treat RR/MDR-TB.[3] These suggestions came after Bdq received conditional and expedited clearances from the European Medicines Agency (EMA) in March 2014 and the US Food and Drug Administration (USFDA) in December 2012; Dlm received conditional approval from the EMA in April 2014.Considering the historically low success rates of treatment and the high incidence of toxicity with traditional RR/MDR-TB treatment plans,[4] There has been hope that following WHO guidelines and gaining access to these medicinal substances could significantly enhance treatment results.[5,6]

Despite significant global efforts, the morbidity and mortality rates linked to tuberculosis (TB) remain high. There are two main elements supporting the current The spread of HIV infection and its correlation with active TB disease, as well as the growing

resistance of Mycobacterium tuberculosis strains to the most potent (first-line) anti-TB medications, are two factors contributing to the TB epidemic.[7]

Population growth, low case identification and cure rates in developing nations, active transmission in overcrowded hospitals, jails, and other public areas, immigration from high-incidence nations, drug misuse, and homelessness are additional factors that have played a role. The primary cause of infection in communities is active illness patients with sputum-positive pulmonary tuberculosis. Even though a strong immune response typically stops M. tuberculosis from multiplying shortly after infection, only 10% of people completely remove the pathogen entirely, whilst 90% merely manage to limit the infection and therefore continue to be latently infected.[8] According to estimates from the World Health Organization (WHO), around one-third of the world's population currently possesses M. tuberculosis, and 5–10% of those infected will go on to acquire active TB disease in their lifetime. However, the lifetime risk for HIV-coinfected individuals is 50%, and the chance of getting active illness is 5–15% annually.[9].

The development of contemporary Mycobacterium tuberculosis (Mtb) sublineages closely corresponds with the various waves of the disease, which has been a major human pathogen from the beginning of modern human existence of people moving out of Africa.[10] By the turn of the 20th century, Mtb was one of the main causes of death, having spread more readily as the human race started to create larger population centers, which led to urbanization. Beginning with streptomycin in 1946 and continuing research that led to the development of today's frontline treatments for drug-sensitive Mtb, the discovery and introduction of antitubercular medications significantly improved the prognosis for patients with TB.

Notably, Mtb nevertheless caused an estimated 9 million infections and 1.5 million fatalities in 2013 [11] despite having an efficient treatment strategy. As long as the patient complies completely, the current standard of care for drug-susceptible Mtb infection is highly efficient in bacillary clearance. The remaining bacilli that have entered a dormant, slowly replicating latent phase are eliminated by a longer "continuation" phase of RIF and INH after a two-month "intensive" phase of a four-drug cocktail comprising RIF, INH, PZA, and EMB (Fig. 1).The growth of drug-resistant bacteria, a tendency that is growing since these strains are easily transmitted and have low fitness, was a lurking worldwide concern throughout this crisis. expenses related to transmission [12,13]. According to a World Health Organization (WHO) report, 3.5% of naive infections worldwide already exhibited resistance to RIF and INH, the two most effective frontline drugs used to treat the illness, making the infection multidrug-resistant TB (MDR-TB) [11].

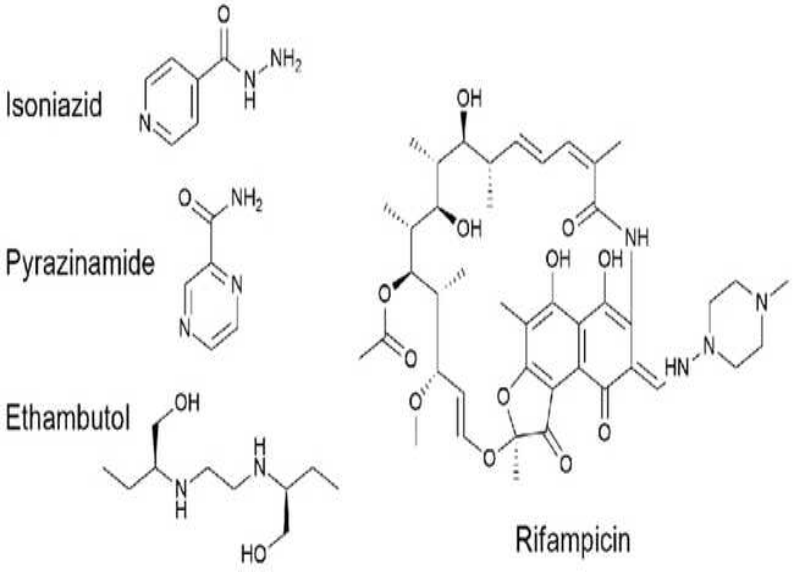


Fig. 1 . Current frontline agents used to treat drug-susceptible Mtb

The term "multidrug resistant tuberculosis" (MDR-TB) refers to resistance to rifampicin and isoniazid, either alone or in combination with resistance to other anti-TB medications. [14] The frequency of MDR-TB About 12% of retreatment cases have , compared to 1-3 percent of new cases. [15,16] Drug-resistant tuberculosis (TB), which is a form of TB resistant to one or more anti-TB medications, is not the same as MDR-TB. Drug therapy must be started in individuals with MDR-TB after a thorough evaluation of their treatment history and careful laboratory testing to determine the strain's susceptibility. The most prevalent way to acquire drug-

resistant organisms is through irregular, insufficient, and incomplete therapy. Another significant contributing factor to the development of medication resistance is poor compliance. Table 1 lists the anti-TB medications. [14]

Groups	Drugs
Group 1: First Line Oral anti-TB agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2: Injectable anti-tuberculosis agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Vincomycin (Vi)
Group 3: Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin,(Lfx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4: Oral second-line anti-tuberculosis agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizidone (Trd); Para-aminosalicylic acid (PAS); Thioacetazone (Th)
Group 5: Agents with unclear role in treatment of drug-resistant tuberculosis	Clofazimine (Cfz), Linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); Thioacetazone (Thz); Imipenem/cilastatin (Ipm/Cln); High dose isoniazid (high dose H); Clarithromycin (Clr)

Table: 1. Classification of anti-tuberculosis Drugs

Clinical experiments have shown that in order to establish a long-lasting and effective cure for tuberculosis, treatment must involve various medications administered over several months. Drug-sensitive (DS) TB is now treated with a six-month standard of care that includes two stages of medication Treatment consists of four medications (ethambutol (E), pyrazinamide (Z), rifampicin (R), and isoniazid (H) administered for two months, followed by two medications (HR) administered for four months. With an estimated 85% treatment efficacy, this treatment has been in use for more than 40 years .[17,18,19] Additionally, it is projected that over 500,000 TB cases each year are resistant to presently used medications, including drug-resistant (DR) and multidrug-resistant (MDR) strains [18]. Due to reduced drug sterilizing capacities and toxicity, treatment for DR TB has historically involved more than four medications administered for up to 24 months. This approach has also been non-standardized and has left many patients with unfavorable results (less than 50% cure) .[20] More effective TB treatments could be developed in light of the creation of new antibiotics, innovative clinical trial methods, and encouraging clinical trial outcomes.[21,22] For the majority of DR TB patients, treatment guidelines now suggest a standardized and shorter treatment (HRZE). Thus, there is cause for optimism regarding the development of additional efficacious TB treatment plans utilizing novel medications and innovative design concepts.

"Drug resistance" is a microbiological diagnosis that indicates how a clinical isolate of a particular disease resists a certain set of antibiotics. Introduced in 1946 to treat tuberculosis (TB), streptomycin (SM) and SM-resistant M. tuberculosis were first identified in 1947 through clinical trials involving patients who did not respond to the antibiotic [23,24]. Multiagent chemotherapy for tuberculosis was developed as a result of the identification of this phenomenon, namely nonresponsiveness to monotherapy, and it has been shown to be successful when combined with SM and para-aminosalicylic acid (PAS) [25]. The British Medical Research Council (BMRC) employed isoniazid (INH), which was first launched in 1952, either by itself or in conjunction with SM or PAS.As a result, John Crofton evaluated a three-drug regimen consisting of SM, PAS, and INH, based on the idea that two out of threeFor practically any resistant strain, medications would be accessible [26]. The first reports of multi-drug-resistant (MDR) TB with resistance to INH and rifampicin (RIF) date back to the 1990s, particularly in relation to the New York epidemic in people infected with HIV [27]. As a result, the World Health Organization (WHO) declared a global tuberculosis emergency in 1994.The length of time that second-line TB treatment has been available in a nation is correlated with the prevalence of MDR-TB; higher rates of resistance have been noted in nations where second-line TB treatment has been available for more than 20 years as opposed to those with a shorter treatment availability period [30].

Mycobacterium TB drug resistance that is genetically determined results from spontaneous chromosome mutation. Increased drug resistance is caused by selection of these genetically modified strains as a result of patients' poor treatment adherence and/or doctors' inappropriate or inadequate prescriptions. Overcrowding, delayed diagnosis, and ineffective infection control methods in

tuberculosis (TB) all contribute to the transmission of acquired drug resistance. Every medicine with action against M. tuberculosis can induce microbiological resistance, and in fact, the more active a drug, the more probable it is to result in clinical resistance[28].
A major obstacle to the global control of tuberculosis is multidrug-resistant tuberculosis (MDR-TB), which is characterized by bacillary resistance to at least iso-niazid and rifampicin in vitro .[29]
Along with M. bovis, M. microti, M. canettii, M. africanum, and others, MTB is included within the Mycobacterium complex category[31]. Several genes have been characterized as a result of MTB H37Rv sequence analysis and coding/non-coding area annotation. and proteins in charge of the life cycle of MTB [32]. More than 200 genes (6%) in the MTB genome are required to code for proteins involved in fatty acid metabolism, according to the genomic analysis [33]. This demonstrates how crucial fatty acids are to MTB physiology. The distinct cell membrane structure of MTB, which can function as an impenetrable barrier to external chemicals, is one of its primary characteristics. The asymmetrical lipid bilayer that makes up the MTB cell membrane is composed of glycolipid and wax on the exterior and long-chain fatty acids (mycolic acid) on the inside. The periplasmic environment formed by these inner and outer membranes contains a layer of peptidoglycan that interacts with mycolic acid covalently. Two first-line medications for TB, isoniazid and ethambutol, which function as inhibitors of the formation of mycolic acid, demonstrate that this cell membrane is necessary for MTB biological activity. MTB route [34].
One of the oldest illnesses, tuberculosis is brought on by the bacterial species "Mycobacterium tuberculosis," which has a serious negative impact on the lungs. It is the most often growing organ. Approximately 85% of TB patients report having pulmonary problems. However, the infectious agent that causes tuberculosis has the ability to infect any region of the body, most likely the spine, kidney, and brain. [35] A person infected with TB bacteria does not necessarily get sick. These traits allow TB infection to be divided into two types: (i) latent tuberculosis infection (LTBI) and (ii) tuberculosis (TB) illness.
According to WHO estimates, there are over 2 billion latent TB cases worldwide. India ranks as the nation with the highest number of multi-drug resistance patients . Drug resistance in tuberculosis is becoming increasingly prevalent. There are additional strains of tuberculosis, therefore the drug issue Resistance is rising daily. because certain strains of Mycobacterium have developed resistance to medications like isoniazid and rifampin that are used as first-line treatments. Therefore, it is necessary to update the recommendations for resistance development.

II. WHAT IS THE MEANING OF MDR-TB OR RESISTANCE TUBERCULOSIS?

As the prevalence of MDR-TB rises, it is difficult to The world urgently needs to contain it before it spreads to another level of TB medications. Multidrug-resistant (MDR) TB occurs when a patient has TB strains and is resistant to the medication (antibiotics) used as first-line treatment. The best antibiotics for these first-line therapies are isoniazid and rifampicin. India accounts for 24% of drug-resistant tuberculosis, followed by China (13%), and Russia (10%). The top three nations are listed here. In India, MDR-TB is extremely frequent and is caused by incorrect medicine and an insufficient TB course. According to reports by Buczynski et al.[36] in December 2014 and Jen et al. [37] in February 2016, 58% and 44/72, 61% of patients, respectively, experienced at least one kind of mistake. The most frequent kind of inaccuracy was linked to first-line medication dosages. They even discovered that 85% of mistakes were still made while patients were in the hospital. For MDR-TB, the WHO advised rigorous chemotherapy in 2016 along with certain TB medications. There is evidence linking resistance to anti-tuberculosis medications, procedures, and molecular techniques to mutations that impact the expression and function of chromosome-encoded targets. [38,39] We updated the most recent data available on MDR-TB diagnosis, management, and prevention.

A. *Goal*

1) Examine current advancements in the study of multidrug-resistant TB.
2) To examine and describe the drug resistance mechanism. detailed description of the drug resistance mechanism.

B. *Causes of TB Resistance*

There are two categories of factors that influence the rate of bacterial mutation: (i) cellular mechanisms factors, includingmismatch repair, microsatellites, drug resistance-granting mutations, mistranslations, and error-prone DNA polymerases
(ii) the host environment, smoking, antibiotics, anti-retroviral medications, (discussed in depth in [40]).
Drug resistance can be classified as either acquired or primary (transmitted). Acquired MDR-, XDR-, and TDR-TB develops by a complex mechanism. The health care system (including DST, antimicrobial medications, control initiatives, and access to medical facilities and medication quality), the patient (e.g., co-infections, individual pharmacokinetics [41], therapy adherence), and the

treating physician (e.g., drug type, dosage, interactions, and length of treatment). Additionally, patients who test positive for M. tuberculosis may develop resistance if anti-TB medications are used to treat other bacterial diseases [42].

Primary drug-resistant TB is caused by the direct spread of drug-resistant M. tuberculosis strains, which leads to primary TB illness. This has been thoroughly established by contact tracing and molecular epidemiology, confirming that M. tb strains are transmitted.

The majority of people who develop XDR-/TDR-TB appear to have received anti-TB medication in the past. Despite the fact that the Prior to "growing out" and producing more resistant versions of the disease, a tiny percentage of the bacilli may survive as "persisters" and develop drug resistance after the medication-induced pressure is removed. When second-line medication treatment is started, this frequently happens in a sequential manner, with progressively greater resistance being developed over time.

In fact, one of the biggest risk factors for developing XDR-TB is prior use of second-line anti-TB medications, if left untreated [48].

Acquired antibiotic resistance examples Among the mechanisms are enzymatic resistance, drug target modification, chemical drug modification, and passive resistance. drug expulsion by efflux pumps, epigenetic drug tolerance, matic drug breakdown, and molecular mimicry of drug targets [43]. The stability and subsequent spread of the resistance phenotype are determined by the acquired antibiotic resistance mechanisms, which frequently lead to a decrease in the fit of the resistant M. tuberculosis mutants. Compensatory mutations, on the other hand, may stabilize the growing resistance phenotype and improve transmission among common populations by restoring the fitness of the resistant strains [44,45].

Numerous elements impact the microenvironment at the location of tuberculosis disease, including the immune response profile, the degree of inflammation, and oxygen availability and cellular necrosis. These elements are essential for both the selection of resistant M. tb strains and the rates of M. tb mutations. Because M. tb adapts to stress by upregulating error-prone polymerases, Jenkins et al. observed a higher M. tb mutation rate at low pH [46]. The transcriptional patterns of M. tuberculosis isolates from the cavity wall, pericavity tissue, or seemingly healthy tissue varied. Changes in transcription, such as the transcriptional activity of drug efflux pumps in M. tuberculosis (reviewed in [47]), represent another environmental-related, non-genetic cause of drug resistance.

III. DRUG-RESISTANT TB (DRTB): CHALLENGES AND NEED FOR INNOVATION

DRTB continues to be a major worldwide health issue, presenting obstacles to patient care and TB control initiatives. Treatment history, health care infrastructure, and socioeconomic circumstances are some of the variables that affect the prevalence of DRTB, which differs by area. [49]

Through better case detection, medication susceptibility testing, and prompt treatment initiation, the World Health Organization's (WHO) End TB initiative seeks to end the worldwide TB pandemic by 2035. [50] The WHO Global TB Report 2022 estimates that 450,000 instances of rifampicin-resistant or multidrug-resistant TB (MDRTB/RRTB) occurred worldwide in 2021. Compared to the previous year, when there were 437,000 incident cases in 2020, this figure indicates a 3.1% increase. Interestingly, RR/MDR-TB spreads largely through direct transmission. [51] DRTB is associated with risk factors such as prior medical treatment, hospitalization, incarceration, and HIV infection. Children are susceptible to DRTB as well. [52] The diagnosis of DRTB has been completely transformed by molecular technologies like DNA sequencing, which have benefits over culture-based testing like quicker results and the capacity to evaluate medication resistance. [53]

From 2010 to 2019, trends in the incidence rates of extensively drug-resistant TB (XDRTB) and MDRTB worldwide were examined. XDRTB rates was mostly constant, whereas the age-standardized rate (ASR) of MDRTB declined by an average of 1.36% year. While XDRTB trends rose, MDRTB trends declined in the majority of regions. Certain age groups had greater incidence rates, while regions with higher sociodemographic indices tended to have lower MDRTB ASRs. [54]

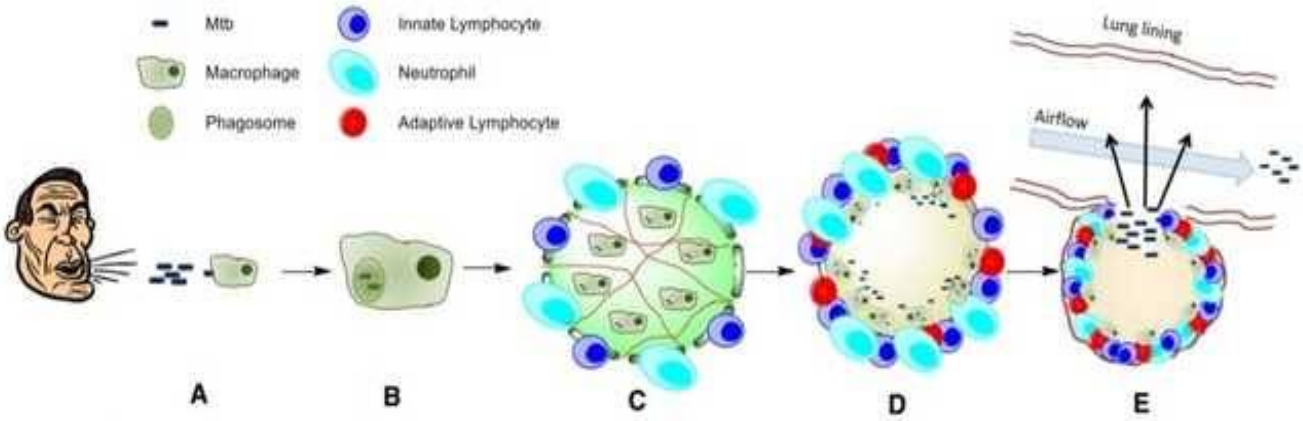
DRTB is a serious issue in India. In India, there are 124,000 MDRTB/RRTB cases, or 9.1% of the total population. [55]The first nationwide investigation on anti-TB drug resistance found that 28% of TB patients were drug-resistant to any therapy (22% of new cases and 36.82% of cases treated previously) (2.84% among new and 11.62% among previously treated [PT]), while 6.19% of TB patients had MDR-TB. Furthermore, RR-TB is largely caused by isoniazid resistance (16% overall, with 11.6% in new cases and 25% in PT). [56]

A major and expanding global issue is the effect of DRTB on public health. The term "DRTB" describes TB bacterium strains that have developed resistance to common anti-TB medications, making the illness more difficult to treat and manage. The following are important details regarding how DRTB affects public health:

• Threat to global health: DRTB TB has a significant role in global antimicrobial resistance, which poses a serious risk to the security of global health. It has significant effects on public health systems and jeopardizes TB control initiatives. [57]

• Higher morbidity and mortality: DRTB results in longer and more involved treatment plans, which frequently have worse patient outcomes than drug-sensitive TB. Patients with DRTB incur substantial financial and social expenses during their therapy, and the mortality rate is higher. [57]
• Limited access to high-quality care: Only one in three patients with DRTB receive the required treatment, making access to high-quality care a persistent barrier. The patients who are absent cause a void in TB control initiatives and impede the disease's growth. [58]
• Financial burden: DRTB treatment is expensive for both patients and healthcare systems. The necessity for specialized care, costly medications, and the length of treatment all add to the financial strain of managing DRTB. [59]
• Dissemination of drug-resistant strains: DRTB has the ability to travel both domestically and internationally, aiding in the spread of resistant strains throughout the world. This presents difficulties for attempts at disease prevention and control, necessitating global cooperation. [60]
• Socioeconomic drivers: In certain areas where poverty, limited access to healthcare, and other socioeconomic factors are prevalent, DRTB can arise and spread. and little resources add to the burden of sickness. [59]
• Difficulties with diagnosis and treatment: DRTB poses particular difficulties with diagnosis and treatment. Although improved detection and monitoring are being achieved with the development of newer diagnostic techniques and genome sequencing technology, access to and coverage of these tools are still restricted in many areas. [61]
• Public health emergencies: Efforts to assist TB patients in continuing their treatment may be hampered by public health emergencies, such as the coronavirus disease 2019 (COVID-19) pandemic. To maintain continuity of care, TB programs need to adjust to possible changes in available resources and offer substitute ways to deliver treatment. [62]
DRTB is a serious public health concern that affects access to high-quality care, economic burden, and global health security. In order to tackle the DRTB problem, sustained funding for surveillance, research, and creative approaches to successfully manage and prevent the illness. To properly address this global health issue, cooperation between governments, international organizations, and healthcare systems is essential.
MTB will change and become resistant to the most widely prescribed anti-TB medications. In particular:
• MDRTB: This strain is resistant to first-line medications, primarily rifampicin and isoniazid. Chromosome gene alterations are frequently the cause of the resistance. [63]
• XDRTB: This strain is immune to fluoroquinolones (levofloxacin and moxifloxacin [MFX]), yet it exhibits resistance comparable to MDRTB. Additionally, second injectable medications including capreomycin, kanamycin, and amikacin. XDRTB is more difficult to treat and frequently arises from inappropriate management of MDRTB patients. [63]
• Completely drug-resistant TB: This severe type of TB resistance is frequently incurable and presents a major health risk. [64]

IV. MYCOBACTERIUM TUBERCULOSIS (MTB) LIFE CYCLE AND MICROENVIRONMENTS



A.) Initial transmission via aerosolized active mycobacterium. Initial bacterial load met by macrophages and phagocytosis occurs to quell the infection.
B.) Mtb inside the phagosome of the host macrophage. Nutrient deplete environment where Mtb relies on host carbon sources like cholesterol degradation and the MCC
C.) The initial immune response to wall off infected macrophages inside a granuloma using inflammatory response cells. Containment is successful for 90% of immuno-competent patients. Immuno-suppression can lead to rapid dissemenation. Granuloma still well vascularized.
D.) Necrotic granuloma where Mtb begins to seep out of the macrophages into the extracellular caseum layer. Vasculature has been choked out by thick caseum layer. This phase can last decades or until host becomes immuno compromised
E.) Eventual granuloma rupture that allows Mtb to escape into the airways and repropagate the cycle and infect others.

Fig.3 Simplified depiction of the Mtb lifestyle

The risk of contracting Mtb infection starts with pulmonary exposure, which happens after inhaling active bacilli from the surrounding environment. A carrier's coughing exposes Mtb to the air, releasing small droplets from their lungs that contain a small number of individual organisms (<10) that must be inhaled deeply into the lungs.

Other factors that are linked to contracting Mtb infection include population density, weather, duration, and intensity of exposure to the Mtb (crowded living and work environments with poor ventilation), a set of virulence factors specific to the infecting organism, and the relative immunocompetency of the would-be host .

At this stage, the lung's host macrophages try to phagocytize the infection (Fig. 3A) and move it through the alveolar epithelium and into the lung. This sets off a pro-inflammatory reaction. response that will enlist additional immune cells to create an encapsulated granuloma, a common immunological reaction to an infection. At this stage, the majority of the bacterial load is contained within what are now known as foamy macrophages (Fig. 3B), which start to line the granuloma's exterior. The granuloma is highly vascularized and packed with immune cells when it first forms (Fig. 3C), which supports the host's immune system's ability to fight the infection and the ability of medications to reach the infection site.The exterior wall of the granuloma hardens into a thick fibrous capsule as it continues to mature against the immune system's unrelenting attack, while the inner core is walled off from the immune cells. The lesion's outside is lined with foamy macrophages, cells die, and caseum forms at its center, cutting off the remaining blood vessels. The granuloma is now regarded as necrotic, and the bacteria are extracellular in this caseum and have the ability to go into a mostly quiescent state (Fig. 3D). Drug penetration is hampered by necrotic granuloma lesions, commonly referred to as tumors, and mice infection models that do not replicate this intricate pathophysiology are inadequate stand-ins for the human illness. The granulomas will fuse to the lungs' airways and rupture after years or in situations when the immune system is compromised, allowing the pathogen to move to new tissue and hosts. (Figure 3E) .[65] There are distinct microenvironments at each stage of the Mtb life cycle that may influence medication susceptibility. Depending on the replication stage (latent vs. actively replicating), the drug's ability to penetrate tissues and membranes necessary to reach the mycobacteria, and variations in blood flow, oxygen levels, and pH in intracellular and extracellular fluids, for instance, can all have an impact on the ionization or activation of drugs. Drug targets in Mtb may also be turned off.

A. Preventive Interventions

Podany and Swindells (2016) outline a variety of innovative treatment approaches and prophylactic measures to systematically prevent the occurrence of TB, MDR-TB, and XDR-TB outbreaks [66]. For instance, they suggest increasing the dosage of rifampicin beyond the standard 600 mg requirement to improve the therapeutic outcomes for MDR-TB patients. Clinicians should try to shorten the recovery period for MDR-TB patients while setting up elevated-dose combinations of potential medications such as

bedaquiline, delamanid, clofazimine, linezolid, and rifampin [66]. However, prospective clinical trials must be conducted to assess the efficacy of these medication combinations for MDR-TB patients. The evidence-based research literature heavily emphasizes the improvement of risk assessment techniques to successfully lower the prevalence of MDR-TB and XDR-TB among predisposed patients.It is imperative that the medication susceptibility studies be drastically improved through observational studies and clinical trials. Additionally, the researchers need to adapt the Bacillus Calmette-Guerin (BCG) vaccine to make it easier to administer to HIV patients in order to lower their risk of tuberculosis and MDR-TB [67]. Furthermore, to successfully raise the caliber of TB/MDR-TB/XDR-TB testing in different medical settings, the development of molecular geneticmethodologies, quick diagnostic techniques, and laboratory information management systems is necessary. [68] To increase the general public's understanding and awareness of tuberculosis, physicians and nurses should start a variety of educational programs in hospitals and the community. The findings and supporting data from the study that was presented Based on clinical literature, it is necessary to increase the standard of preventive/prophylactic measures through clinical research in order to reduce the incidence and spread of MDR-TB in high-risk patients.

B. Diagnosis of drug-resistant TB, MDR-TB, and XDR-TB

Traditional DST techniques identify M. tuberculosis growth on solid (Lowenstein-Jensen) medium using one of three techniques (absolute concentration, resistance ratio, or proportion method) in the presence of antibiotics; nevertheless, it takes two to four weeks to acquire primary culture data. Now commonly employed for first- and second-line anti-TB DST of M. tuberculosis, broth-based fully automated culture methods (such the Bactec MGIT 960 TB system) provide results from a primary culture in 5–8 days [77]. The Bactec MGIT 960 system, which accurately diagnoses MDR-TB infections in 8–10 days, has also recently shown direct DST with smear-positive specimens for INH and RIF [69].

For the DST of M. tuberculosis in environments with limited resources, straightforward, low-cost, non-commercial phenotypic techniques have also been devised [70]. These The nitrate reductase (NR) assay, thin layer agar (TLA) method, colorimetric redox indicator (CRI) approaches, phage-based assays, and microscopic observation drug susceptibility (MODS) test are among the techniques. The WHO has approved the MODS, NR, and CRI tests among these techniques . [70 ,77,78,79]

24-well plates are used for the MODS test. An inverted microscope is used to detect the recording growth of M. tuberculosis after sputum is directly inoculated into Middlebrook 7H9 broth that contains first-line anti-TB medications. Results are obtained in 7–9 days and show ≥95% agreement with conventional DST for INH, RIF, and MDR-TB. Many samples can be analyzed. The MODS assay is modified by the thin layer agar (TLA) method to detect MDR-TB and XDR-TB in cultures [70]. Because live M. tuberculosis reduces nitrate to nitrite, typically after 7–10 days, the NR assay detects a pink-red hue. MDR-TB and XDR-TB can be detected with a sensitivity of ≥95% and a large number of samples can be processed. The rare nitrate reductase-negative M. tuberculosis cannot be detected by the NR assay, which only detects bacterial growth, potentially leading to false-positive results [70]. The CRI techniques work by lowering markers such tetrazolium salts and resazurin, which are added to culture media when anti-TB medications are present. Typically, results are accessible in 8–10 days. The detection of MDR-TB and XDR-TB strains has been assessed using these techniques [70].

Mycobacteriophages are used in phage-based assays to use a phage amplification test or the more sensitive luciferase reporter mycobacteriophages to identify the growth or presence of M. tuberculosis, whether anti-TB medication is present or not. When luciferin is present, viable M. tuberculosis that is developing in the presence of anti-TB medications emits light, indicating that it is a drug-resistant strain [85].

Within one to two days, molecular techniques can identify resistance-associated mutations in M. tuberculosis target genes. The two clinical isolates of M. tuberculosis, and clinical samples that are smear-positive (and occasionally smear-negative) are utilized to quickly identify MDR-TB and XDR-TB [80]. Since 90–95% of RIF-resistant organisms have mutations in the 81-bp RRDR of the rpoB gene, RIF resistance is easy to detect. Since 85–90% of isolates of M. tuberculosis that are resistant to RIF are also resistant to INH, RIF resistance detection also detects the majority of MDR-TB strains [83]. Resistance to RIF and, consequently, the majority of MDR-TB strains are simultaneously detected by certain molecular assays for TB diagnosis (Xpert MTB/RIF) [81,82]. For various medications, the sensitivity of resistance detection varies significantly. Even with the recent development of molecular assays that target numerous gene loci, not all strains that are resistant [80]. Using fluorogenic probes or high-resolution melting curve analysis of RT-PCR amplicons, real-time PCR (RT-PCR) assays identify MDR-TB and XDR-TB strains in clinical specimens and/or culture isolates by detecting dominant mutations that confer resistance to INH, RIF, SM, KAN/AMI/CAP, and FQs [71,80].

MDR-TB has also been detected using PCR amplification of target areas, followed by amplicon sequencing or pyrosequencing. XDR-TB strains in clinical specimens and culture isolates. M. tuberculosis strains resistant to INH, RIF, EMB, PZA, and INH +

RIF (MDR-TB) were found in 64%, 96%, 69%, 100%, and 50% of sputum samples (containing smear-negative and culture-positive samples) by direct DNA sequencing analysis, respectively [72]. Complete genome sequencing may soon become commonplace, allowing the identification of resistance-conferring mutations in several target genes of MDR-TB and XDR-TB strains, even if it is now impractical with clinical specimens [73].

Additionally, three commercial line probe assays based on reverse hybridization have been created. M. tuberculosis is detected by INNO-LiPA Rif. TB, along with its resistance to RIF, but it can also forecast around 85–90% of M. tuberculosis strains' MDR status. For the detection of M. tuberculosis from sputum samples that are smear-positive and smear-negative, respectively, pooled sensitivities of approximately 93% and 65% have been reported. For smear-positive and smear-negative sputum samples, the pooled sensitivities for RIF resistance detection were 88–97% and 77–99%, respectively [80]. RIF and INH resistance (MDR-TB strains) in culture isolates and sputum samples are identified using the Genotype MTBDRplus assay [80,84]. Smear-negative pulmonary and extrapulmonary specimens have a lower sensitivity for M. tuberculosis detection than smear-positive samples, which have a sensitivity of 78–98% [74,80]. In culture isolates and smear-positive sputum samples, the pooled sensitivity for RIF resistance is approximately 98%, but it is approximately 89%for INH resistance in clinical specimens and significantly lower in cases with culture confirmation. According to reports, the sensitivity for detecting RIF + INH resistance (MDR-TB) in culture isolates and smear-positive sputum samples ranges from about 85 to 90% [74,80]. In culture isolates and clinical specimens, the genotype MTBDRsl assay identifies resistance to FQs, injectable medications (KAN/AMI/CAP), and EMB [80]. According to reports, the genotype MTBDRsl's pooled sensitivities for detecting resistance to FQs, KAN, AMI, and CAP were 85%, 83%, 90%, and 87%, respectively [75,80]. In high-prevalence situations, the combination of genotype MTBDRsl and genotype MTBDRplus shortens the time to diagnosis of XDR-TB by detecting XDR-TB strains [76].

V. RECENT DRUG APPROVALS AND TREATMENT REGIMENS

A. *Bedaquiline (BDQ)*

Adult patients with pulmonary MDRTB may benefit from combination therapy using the diarylquinoline medication BDQ. [86] It is the first medication created especially to treat tuberculosis in more than 40 years.

In December 2012, the FDA issued an accelerated approval based on an examination of two phase 2 trials' time to sputum culture conversion. [87] In one trial, patients receiving BDQ for the first 24 weeks saw faster and longer-lasting conversions, demonstrating clinical efficacy. [88] In June 2013, the WHO released interim policy guidelines for BDQ along with MDRTB treatments that were recommended by the WHO. [89] The National TB Elimination Program and Programmatic Management of Drug-Resistant TB services in India have authorized BDQ-containing regimens for the treatment of DRTB. Since BDQ is currently used in all facilities, medical professionals need to understand its importance in the treatment of DRTB. [90]

By blocking the proton pump of mycobacterial adenosine triphosphate (ATP) synthase, BDQ demonstrates particular antimycobacterial action. This enzyme binds and is essential for cell life. Bacterial death results from exposure to mycobacterial ATP synthase at subunit c. With almost 20,000 times the affinity of human mitochondrial ATP synthase, BDQ binds to mycobacterial ATP synthase, causing little host cell harm and selective activity in mycobacteria. [86] BDQ kills both dormant and actively proliferating mycobacteria. It inhibits both drug-sensitive and drug-resistant mycobacteria. BDQ strongly inhibits a variety of non-tuberculous mycobacteria (NTM), including as Mycobacterium avium, Mycobacterium ulcerans, Mycobacterium abscessus, and Mycobacterium intracellulare. BDQ has a modest inhibitory effect on both Gram-positive and Gram-negative bacteria. [86]

When taken with food, BDQ has higher absorption and linear pharmacokinetics, which increase in serum drug levels. It undergoes hepatic metabolism, with N-monodesmethyl-BDQ (M2) being the primary metabolite. BDQ is well linked to plasma proteins and has a large volume of distribution. Its sluggish release from peripheral tissue compartments results in a slow terminal elimination profile with a half-life of roughly 5.5 months. [91]

In one out of every 108 cases, BDQ-resistant mutations arise due to two mechanisms: atpE gene mutations and efflux pump expression. Mutations in the atpE gene at locations 63 and 66 affect BDQ's capacity to bind to the c subunits of the ATP synthase enzyme. Both the rapidly growing Mycobacterium novocastrense and the slowly growing NTMs have atpE gene variations that promote BDQ resistance. The efflux pump expression is caused by mutations in Rv0678, which are responsible for BDQ heteroresistance in MTB. When there is no indication of cross-resistance with other antitubercular medications, a phenomenon known as heteroresistance occurs when bacterial isolates have populations that are both more susceptible to and resistant to antibiotics. [92]

Headache, nausea, vomiting, diarrhea, abdominal discomfort, limb pain, arthralgia, back pain, and dizziness are examples of adverse drug responses that may occur from using BDQ. There Hemoptysis, pleuritic discomfort, rash, pruritus, acne, pharyngolaryngeal

pain, deafness, hyperuricemia, QT interval prolongation, elevated transaminases, and hemoptysis have also been reported. [93] QT prolongation, a risk factor for sudden death and a biomarker for ventricular tachyarrhythmias, can be brought on by BDQ. Avoid using medications that lengthen the QT interval concurrently as this could result in additive QT prolongation. [93] Hepatotoxicity can also be brought on by BDQ, and other dangers may arise from hepatotoxic illnesses and drugs. Although BDQ drug susceptibility testing is not yet standardized, laboratory testing indicates that a break threshold for susceptibility of less than 0.5 µg/mL in agar medium .[94]

It is not advised to use BDQ in old patients, pregnant women, children, or those with extrapulmonary illness. Information about its use in people with HIV is scarce, and No obvious pattern or reason can be found. [95] In a trial with a placebo, the BDQ treatment group died at a rate of 11.4% whereas the placebo group died at a rate of 2.5%. There is no indication in the data that QT prolongation played a role in the deaths of the BDQ group. When using BDQ, considerable caution is advised until a comprehensive safety profile is established, even in the absence of any obvious trend or reason. [95]

B. Delamanid (DLM)

DLM was approved by the European Medicines Agency as a first-in-class bicyclic based on promising phase IIb study results. For the treatment of MDR-TB, nitroimidazole. Owing to its rapid resistance acquisition, it has been used in 54 and 89 countries, respectively. In addition to appropriate use and drug resistance monitoring, combination therapy with additional anti-TB medications is recommended to prevent resistance. [96]

DLM is a prodrug that produces nitrous oxide and inhibits the manufacture of methoxy and keto MA via the mycobacteria F420 system, hence conferring mycobactericidal action. The way that DLM and isoniazid work is by blocking the production of mycolic acid, which is essential to the mycobacterial genus' ability to survive.

It is believed that DLM inhibits the formation of mycolic acid mostly through the reactive intermediate metabolite. When this crucial element is extracted from the cell wall, the Mycobacterium is eliminated.[97]

Regarding strains of MDRTB and XDRTB, DLM has demonstrated activity in vitro. It is ineffective against NTMs and is a limited-spectrum antibiotic.

It has been proposed as a treatment for tuberculosis because of its antagonistic action and lack of cross-resistance with other drugs. Non-synonymous mutations in five genes—ddn, fbiA, fbiB, fbiC, and fgd1—can result in DLM resistance. For the biosynthesis and modification of F420, these genes generate proteins and coenzymes. Bicyclic nitroimidazole medications are changed into intermediate metabolites and desnitro forms of DLM by the activation of F420 by the ddn gene. [98]

Because DLM absorbs better with food than first-line anti-TB medications administered on an empty stomach, oral treatment is advised. The highest level of concentration is noted. after four to five hours. After stopping, it has a half-life of 38 hours. After 10–14 days, steady-state concentration happens. Due to its poor water solubility and restricted absorption at higher doses, early investigations revealed that DLM exposure was not proportionate to dosage, plateauing at 300 mg. [97]

In clinical trials, the treatment group experienced a dose-dependent, considerably greater incidence of QT prolongation than the placebo group. It was modest to moderate in intensity and did not accompany signs of arrhythmia or syncope. Clinical testing revealed no significant side effects. [97] According to in vitro studies, the drug has no effect on cytochrome P450 (CYP 450) enzymes at the expected therapeutic dosages. No significant interactions between DLM and anti-retroviral drugs such as tenofovir,lopinavir/ritonavir, and efavirenz. Because it enables the safe combination of DLM with other anti-TB drugs, this is a desirable feature. [99]

C. Pretomanid (PA)

PA a newly discovered anti-mycobacterial drug made from nitroimidazole, with potent bacteriostatic and bactericidal properties effects in addition to possessing an excellent profile of effectiveness and tolerability. PA is a prodrug that targets MTB in two ways: anaerobically generating des-nitro metabolites and nitric oxide, which inhibit cytochrome c oxidase and lower ATP concentration in cells, and aerobically blocking protein and lipid synthesis. The effectiveness of linezolid and rifampicin against latent phenotypic MTB is similar to that of PA against non-replicating mycobacteria.[100]

PA needs to undergo phase I and II biotransformation via a number of metabolic processes. It has a mean Tmax of 4-5 hours, a steady state in 5-6 days, and an elimination half-time of 16-20 hours. With a Vd/F of 92–180 mL, PA diffuses into the body and binds to albumin in a modest way. Its lengthy half-life and efficient tissue absorption allow for a single daily dosage. PA is able to pass through the blood-brain barrier. Cytochrome CYP3A is responsible for 20% of its metabolism. [100]

Headache, skin or subcutaneous tissue problems, hepatic disorders with elevated ALT and AST, and gastrointestinal symptoms are among the side effects of PA treatment. QTc Studies assessing adverse events during PA monotherapy did not find prolongation, although more investigation is required. Although there have been reports of reversible increases in serum creatinine levels, they are thought to be unrepresentative of renal function .[100]Preclinical research also documented transient liver enzyme increase, which was verified in patients on PA-containing regimens.[101] Male rats given PA showed testicular damage, however there was no documented impact on male human fertility. Male trial participants' levels of sex hormones were consistently within range. [100]
Following positive results from a phase III trial, PA was approved by the US FDA in August 2019. For the treatment of individuals with pulmonary extensive DRTB, this oral active drug has been authorized for use. MDR TB intolerant or nonresponsive as part of the BPA regimen (bedaquiline, pretomanid, and linezolid).[102]
In order to treat rifampicin-resistant (RR), multidrug-resistant (MDR), and pre-XDRTB with BDQ, LZD, and MFX in a 6-month period, the WHO advised include PA. program due to promising findings from randomized controlled trials that are now underway and recently published. PA may potentially be a useful treatment for drug-susceptible TB, latent TB infection, and non-tuberculous mycobacteria, though further research is needed. [103]

D. Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin (BPaLM) Regimen

For DRTB, the BPaLM regimen is an all-oral treatment. especially made for people with MDRTB/RRTB. Four medications are combined to form it: BPaLM. Numerous studies have examined the BPaLM regimen, which has demonstrated encouraging effects in terms of both safety and therapeutic outcomes.[104]
In terms of the primary composite outcome after 72 weeks, the TB-PRACTECAL research indicated that the BPaLM regimen was not inferior to the standard-care treatment and even outperformed it.
Further confirming the BPaLM regimen's potential as a more patient-friendly and successful treatment option for rifampin-resistant pulmonary tuberculosis, it also demonstrated a better safety profile. [105]
In the Phase 3 Nix-TB trial in South Africa, the BPaLM regimen was clinically investigated and showed positive results in 90% of patients after six months of therapy, with a nine-month extension. Patients who were co-infected with HIV were also enrolled in the research, and encouraging outcomes were seen in this group as well.[106]
Research has indicated that rifampin-resistant pulmonary tuberculosis can be effectively treated with the BPaLM regimen.
When compared to the standard-care treatment for rifampin-resistant TB, the BPaLM regimen demonstrated superiority and non-inferiority in a randomized trial. It demonstrated an improved safety profile, which is essential for controlling side effects in DRTB patients. [100]
In the 2022 revision of their Consolidated Guidelines on TB, the WHO recognized the promise of the BPaLM regimen and incorporated it. In accordance with the rules, For MDR/RR-TB patients who have further resistance, the BPaLM regimen is advised; for those who do not have fluoroquinolone resistance, a 9-month all-oral regimen is advised. The guidelines offer an operational guidebook for implementation and are intended to enhance care and treatment for people with DR-TB. [107]
The impact and cost-effectiveness of the BPaLM regimen for treating RRTB were assessed in the Moldovan study. According to the analysis, the BPaLM regimen potentially preservecomparable treatment results while lowering lifetime expenditures per patient in comparison to the conventional 9- or 18-month approaches.[108] According to this cost-effectiveness analysis, the BPaLM regimen presents a viable substitute for the management of TB that is resistant to rifampin. It is important to remember that although the BPaLM regimen appears to be a viable and affordable treatment option for DRTB, more investigation is required to evaluate its application in particular contexts.
All things considered, the BPaLM regimen is a major step forward in the treatment of DRTB, providing patients with MDR/RR-TB with optimism for better clinical results and a higher quality of life. It is encouraging for the global fight against DRTB that this regimen is included in the WHO guidelines and that it has a beneficial effect on patients' health.

E. Sutezolid

The antimycobacterial qualities of sutezolid are being investigated, especially in relation to the treatment of TB and DRTB. It is a member of the oxazolidinone class of antibiotics and has been studied for its ability to prevent the start of protein synthesis, which would have a bactericidal effect on MTB, the TB-causing pathogen. [109]
To combat MTB, studies have shown that sutezolid has a potent bactericidal action. It has been investigated in patients with positive sputum smear results, where several dosage schedules were assessed. Both the treated patients' sputum and whole blood cultures showed bactericidal action. There was no significant liver damage, despite the fact that some patients had brief ALT increases.[110]

Pfizer Inc. has sold the rights to develop and market sutezolid to Sequella, a pharmaceutical firm that specializes in developing new antibiotics. Sequella wants to develop the Phase 2 oxazolidinone antibiotic sutezolid for the treatment of tuberculosis. Sequella's ongoing Phase 2 trials for drug-sensitive and MDRTB are in line with the purchase. Combining sutezolid with SQ109, another medication in Sequella's pipeline, has the potential to completely transform the way that tuberculosis is treated in all of its manifestations.[111]

VI. CONCLUSION

MDRTB poses a threat to TB eradication and a significant barrier to TB control worldwide. Better handling of vulnerable TB cases, as well as the detection and management of the majority of MDRTB patients are necessary to keep this epidemic under control. Improvements in the treatment of DRTB have led to shorter MDRTB regimens and the availability of new or repurposed drugs including BDQ DLM, clofazimine, and linezolid. For all TB patients, including those who are both sensitive and resistant to current treatments, the goal is to develop a universal new regimen. Reducing complications and maintaining high cure rates require a shorter duration of treatment. The global TB community, which includes funders and legislators, must work together to ensure that patients who require these drugs can have them.

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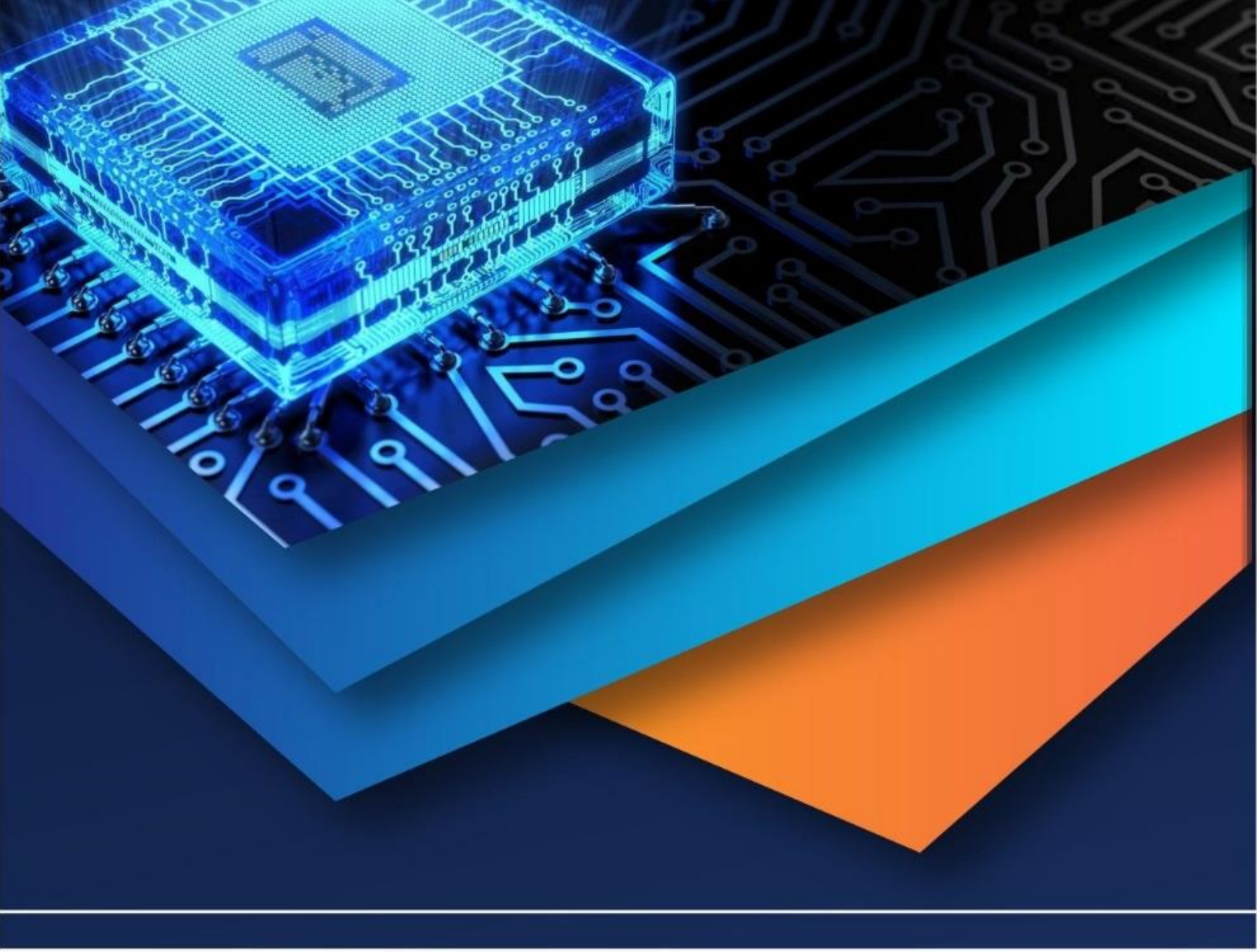

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