IJMPR 2025, 9(2), 63-66

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 6.669

"A NEW HORIZON IN MDR TB THERAPY: BPALM APPROACH"

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Article Received on: 24/12/2024
Article Revised on: 13/01/2025
Article Accepted on: 02/02/2025

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) continues to pose a significant global health threat, especially in high-burden countries like India. MDR-TB is caused by strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, requiring more complex and prolonged treatment regimens. Conventional treatments for MDR-TB are lengthy and often associated with severe side effects. In response, newer therapeutic strategies such as the BPaL (bedaquiline, pretomanid, linezolid) and BPaLM (BPaL with moxifloxacin) regimens have emerged as promising alternatives. These all-oral regimens, endorsed by the WHO in 2022, offer significant advantages, including a shortened treatment duration of six months, improved efficacy, and fewer adverse effects compared to the traditional 9–11 months of therapy. The combination of bedaquiline, pretomanid, linezolid, and moxifloxacin targets multiple bacterial mechanisms, enhancing the effectiveness of the treatment. These regimens not only reduce treatment time but also lower healthcare costs, improve patient adherence, and contribute to a better quality of life. This paper reviews the epidemiology, pathogenesis, clinical presentation, diagnostic methods, and management of MDR-TB, emphasizing the novel BPaL/BPaLM regimens. These treatments represent a critical advancement in the fight against MDR-TB, offering improved accessibility, cost-effectiveness, and superior treatment outcomes, which are essential for the global elimination of drug-resistant tuberculosis.

KEYWORDS: Multidrug-resistant tuberculosis (MDR-TB), BPaL M regimen, bedaquiline, pretomanid, linezolid, moxifloxacin, tuberculosis therapy, drug resistance, WHO guidelines, patient adherence.

INTRODUCTION

Tuberculosis (TB) is a highly contagious airborne disease caused by bacteria of the *Mycobacterium tuberculosis* complex. It presents as a dynamic spectrum, ranging from asymptomatic latent infection to severe, life-threatening illness. While TB can affect virtually any part of the body, it most commonly targets the lungs (pulmonary TB) where it may cause symptoms like pleuritic chest pain, low-grade fever, prolonged productive cough, haemoptysis, fatigue, loss of appetite, night sweat and weight loss.[1,2,3]

Types of DR-TB

- Isoniazid Mono-Resistant (Hmono)
- Extensively Drug-Resistant (XDR-TB)
- Rifampicin- Resistant TB (RR-TB)
- Pre-Extensively Drug-Resistant (Prexdr-TB)
- Multidrug- Resistant (MDR-TB).[4,6]

MDR-TB: Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis caused by strains of Mycobacterium tuberculosis that are resistant to at least isoniazid and rifampicin, the two most effective first-line anti-TB drugs. This resistance arises primarily from improper use or inadequate administration of anti-TB medications, leading to treatment failure and the development of drug-resistant strains. MDR-TB requires the use of alternative, often longer and more complex treatment regimens, posing significant challenges to disease management and control.[4,5]

Epidemology: India faces a significant challenge in managing multidrug-resistant tuberculosis (MDR-TB), with the second-highest global burden. In 2018, there were 1.3 million cases of drug-resistant TB (DR-TB) in the country. Among new TB cases, 2.8% were identified as MDR-TB, while the prevalence rose to 12% among those who had undergone previous treatment. The estimated incidence of MDR-TB and rifampicin-resistant TB (RR-TB) in India is 135,000 cases.[4,6]

Risk factors for developing MDR-TB

- **Failure of first-line treatment:** Not getting better after completing the initial TB treatment (DOTS WHO Category I or II).

- **Relapse:** Getting TB again after being treated successfully with first-line drugs.
- **Stopping treatment early:** Interrupting or not completing a first-line TB treatment.
- **Contact with MDR-TB:** Being in close contact with someone who has MDR-TB.
- **High-risk settings:** Living or working in places with high MDR-TB rates, such as prisons or hospitals.
- **High-prevalence areas:** Living in regions or countries where MDR-TB is common.
- **HIV infection:** Having HIV, which weakens the immune system and increases the risk of drug-resistant TB.[11]

PATHOGENESIS OF TB: Upon transmission, Mycobacterium tuberculosis (M. tb) enters the lungs and is engulfed by macrophages. Immune cells are recruited to contain the infection, forming granulomas, the hallmark of TB. In healthy individuals, the infection remains latent but carries a risk of reactivation.

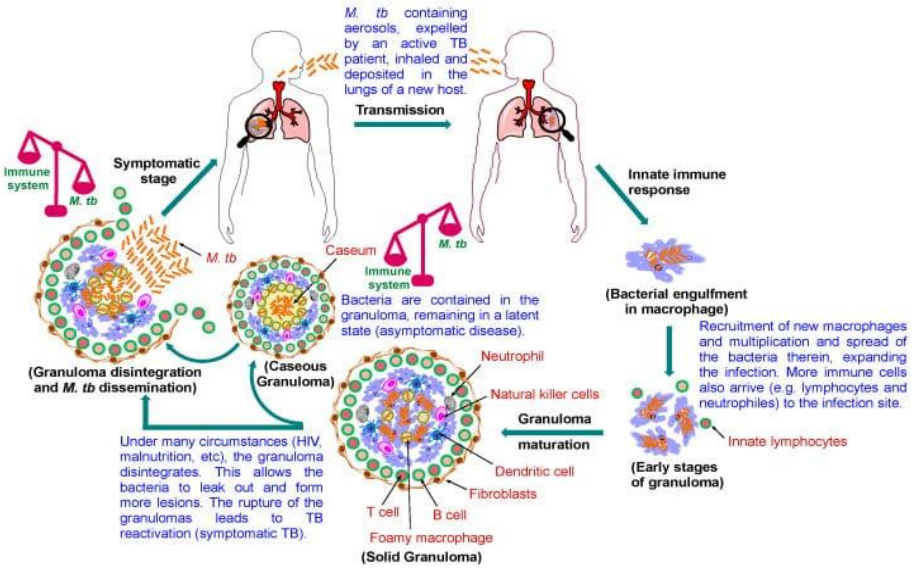

Figure 1: Explains pathophysiology of TB.

Necrosis of foamy macrophages releases lipids, leading to caseation (a cheese-like core) within the granuloma. This weakens its structure, allowing bacilli to seep into the caseum layer. Reactivation triggers rapid bacilli proliferation, causing granuloma rupture. The bacteria spread to airways and are expelled as infectious aerosol droplets, restarting the cycle and infecting new hosts.[3,7,8]

CLINICAL MANIFESTATIONS

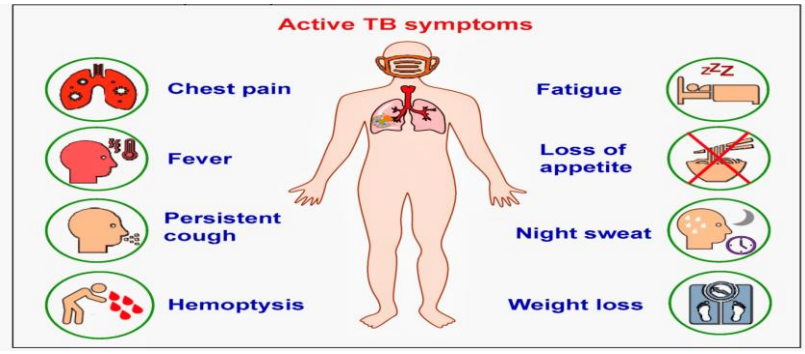

Figure 2: Explains Clinical manifestations.

Diagnosis of MDR-TB

i. Phenotypic (Culture-Based):* Directly tests if the bacteria grow in the presence of antibiotics.
ii. Molecular (Genomic):* Uses DNA to predict resistance but doesn't confirm it directly.

1. Phenotypic Testing

- Performed on a positive culture and provides results in about *14 days*.
- If resistant to first-line drugs, further testing for second-line drugs may take longer.
- Advantage: Offers direct evidence of resistance by showing bacterial growth inhibition.

2. Molecular Testing: Two types

a. Targeted Testing: Looks for specific mutations but can miss or misinterpret mutations. Example: Line probe assays may miss 10% of isoniazid-resistant cases.
b. Whole Genome Sequencing (WGS):
- Examines the entire bacterial genome.
- More accurate in identifying resistance-related mutations.
- Provides faster reports for pan-susceptible strains (no resistance detected).[9,10]

MANAGEMENT OF MDR-TB: Tuberculosis (TB) treatment typically involves a six-month regimen of four primary antibiotics: rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB). This prolonged treatment is often associated with several side effects, including nausea, vomiting, weight loss, hepatotoxicity, skin reactions, gastrointestinal issues, and immune responses, particularly in the case of RIF. Additionally, RIF interacts with INH, another key anti-TB drug, forming an insoluble hydrazine derivative.

Anti-tuberculosis drugs are categorized into two groups:

1. First-line antituberculosis drugs
- Isoniazid (INH)
- Rifampicin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Streptomycin (SM)

2. Second-line antituberculosis drugs

Fluoroquinolones	Injectable antituberculosis drugs	Less effective second-line drugs
● Ofloxacin (OFX) ● Levofloxacin (LEV) ● Moxifloxacin (MOX) ● Ciprofloxacin (CIP)	● Kanamycin (KAN) ● Amikacin (AMK) ● Capreomycin (CAP)	● Ethionamide (ETH)/Prothionamide (PTH) ● Cycloserine (CS)/Terizidon ● P-aminosalicylicacid (PAS).[12,13]

Evaluation of BPALM therapy: The introduction of the 6-month all-oral BPaL (bedaquiline, pretomanid, linezolid) and BPaLM (BPaL with moxifloxacin) regimens marks a significant advancement in the treatment of drug-resistant tuberculosis (DR-TB). These regimens, recommended by the WHO in 2022, offer a shorter, more effective alternative to the previously endorsed 9–11-month standard short oral regimens (SSOR) and 18-month standard long oral regimens (SLOR).[14]

Bedaquiline: Bedaquiline, a diarylquinoline compound with a unique mechanism of action against tuberculosis (TB), received accelerated or conditional approval in the United States in 2012 and Europe in 2014 for the treatment of multidrug-resistant TB (MDR-TB). Interim guidance for its use has been provided by the World Health Organization (WHO). Marketed as SIRTURO®, bedaquiline targets ATP synthase, disrupting bacterial energy production, and exhibits both bactericidal and sterilizing properties. Its effectiveness has been demonstrated in multiple Phase 2 clinical trials and real-world studies involving bedaquiline-based regimens for MDR-TB treatment.[15,16]

Pretomanid: (Pa, PTM), a nitro-imidazooxazine compound, inhibits mycobacterial cell wall synthesis and promotes nitric oxide release. It was recently approved by the U.S. Food and Drug Administration (FDA) as part of the BPaL combination regimen, alongside bedaquiline (BDQ) and linezolid (LZD), for treating adults with pulmonary extensively drug-resistant TB (XDR-TB) or multidrug-resistant TB (MDR-TB) that is either treatment-intolerant or non-responsive.[17]

Linezolid (L), an oxazolidinone antibiotic approved in many countries for treating drug-resistant gram-positive bacterial infections, works by inhibiting bacterial protein synthesis. Resistance of *Mycobacterium tuberculosis* (MTB) to linezolid is rare, as its use in tuberculosis (TB) treatment has been limited. Linezolid demonstrates potent activity against gram-positive bacteria and is an effective option for managing multidrug-resistant (MDR) strains. Since delamanid, bedaquiline, and linezolid have only recently been approved, resistance to these drugs is expected to remain low among TB patients.[18,19]

Fluoroquinolones are key components of MDR-TB treatment regimens, as their use has been linked to improved patient outcomes.[63,64] The World Health Organization (WHO) treatment guidelines emphasize the superior bactericidal activity of later-generation fluoroquinolones, such as levofloxacin, moxifloxacin, and gatifloxacin, compared to older agents like ofloxacin and ciprofloxacin. Successful treatment of MDR-TB requires the development of a regimen comprising multiple agents that are both effective against the infecting organism and possess bactericidal properties.[20]

ADVANTAGES OF BPAL/BPALM THERAPY

Reduced Treatment Duration: By cutting treatment time to six months, these regimens improve patient convenience and compliance while decreasing the risk of treatment fatigue and dropout.

Lower Costs: Shorter treatment durations reduce both healthcare system expenditures and patient-incurred costs, offering a more cost-effective solution for low- and middle-income countries.

Improved Access: Simplified treatment regimens alleviate resource constraints in overburdened healthcare systems, enabling wider access to care.

Enhanced Adherence: The all-oral, shorter duration approach increases the likelihood of patient adherence, leading to better treatment success rates.

Better Quality of Life: Patients benefit from fewer side effects reduced financial burdens, and a quicker return to normal activities due to the shorter, less complex treatment process.

System-Level Impact: By streamlining treatment protocols, BPaL/BPaLM regimens free up healthcare resources, allowing systems to address other pressing needs.[14]

DISCUSSION

Multidrug-resistant tuberculosis (MDR-TB) presents a major global health challenge, especially in high-burden countries like India. Traditional MDR-TB treatment regimens are lengthy and associated with significant side effects, making adherence difficult. The introduction of the BPaL (bedaquiline, pretomanid, linezolid) and BPaLM (BPaL with moxifloxacin) regimens offers a promising solution. These all-oral regimens, recommended by the WHO in 2022, significantly reduce the treatment duration to six months, improve efficacy, and minimize side effects, making them a more patient-friendly and cost-effective alternative.

Bedaquiline, pretomanid, linezolid, and moxifloxacin work synergistically to target different bacterial mechanisms, effectively eradicating resistant strains of *Mycobacterium tuberculosis*. By shortening the treatment period, these regimens reduce both healthcare costs and the risk of treatment fatigue, improving patient adherence and quality of life. Furthermore, the all-oral regimen eliminates the need for injections, further enhancing patient convenience.

These advances not only improve clinical outcomes but also provide a scalable, accessible solution for resource-constrained settings, where MDR-TB is most prevalent. The BPaL/BPaLM regimens could potentially reduce the burden of MDR-TB globally and contribute significantly to TB control efforts.

CONCLUSION

The BPaL and BPaLM regimens mark a significant advancement in MDR-TB therapy, offering a shorter, more effective, and patient-friendly treatment option. Their reduced treatment duration, combined with improved efficacy and fewer side effects, enhances patient adherence and quality of life. The potential for lower treatment costs and improved access to care in resource-limited settings further underscores their importance in the global fight against MDR-TB. As these regimens are integrated into national and international TB control programs, they hold the promise of significantly reducing the global burden of MDR-TB and moving closer to TB elimination goals.

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