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Innovative Horizons in Tuberculosis Management: Tackling Drug Resistance Through Advanced Pharmacotherapies

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Resumen

La farmacología de los fármacos utilizados para tratar la tuberculosis resistente representa un pilar fundamental en la lucha contra las cepas multirresistentes (MDR) y extremadamente resistentes (XDR). El artículo presentado explora los avances recientes en estrategias terapéuticas, incluyendo el desarrollo de medicamentos de segunda línea y agentes innovadores, que ofrecen un renovado optimismo para una intervención eficaz. Se hace hincapié en la comprensión de la eficacia de los fármacos, los perfiles de seguridad y el diseño de terapias combinadas óptimas adaptadas a las necesidades individuales de cada paciente. Además, se destaca la importancia de la colaboración global, la inversión continua en investigación y la innovación tecnológica como pilares esenciales para abordar el creciente desafío de la resistencia a la tuberculosis. Las futuras orientaciones se centran en mejorar la accesibilidad al tratamiento, optimizar los regímenes farmacológicos y fomentar el desarrollo de soluciones sostenibles que se ajusten a los patrones de resistencia en evolución, prometiendo un impacto transformador en los esfuerzos de salud global contra la tuberculosis.

Palabras clave

Tuberculosis, tuberculosis resistente, TB-DR.

Conflicto de intereses

Este artículo no presenta conflicto de interés.

Summary

The pharmacology of drugs used to treat resistant tuberculosis represents a critical cornerstone in the battle against multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. The presented article explores recent progress in therapeutic strategies, including the development of second-line medications and innovative agents, which offer renewed optimism for effective intervention. Emphasis is placed on understanding drug efficacy, safety profiles, and the design of optimal combination therapies tailored to individual patient needs. Furthermore, the importance of global collaboration, continued investment in research, and technological innovation is underscored as essential pillars for addressing the escalating challenge of tuberculosis resistance. Future directions focus on enhancing accessibility to treatment, optimizing drug regimens, and fostering the development of sustainable solutions that align with evolving resistance patterns, promising a transformative impact on global health efforts against tuberculosis.

Key words

Tuberculosis, resistant tuberculosis, TB-DR.

Conflict of interests

This article does not present a conflict of interest.

Introduction

Historical Context

Mycobacterium tuberculosis is the main etiologic agent of Tuberculosis (TB), historically referred to as the 'white plague', which precipitated considerable global mortality throughout the 19th century. However, in the early beginning of the mid-20th century, a marked reduction in tuberculosis prevalence and associated fatalities was observed, particularly in industrialized nations. The reported decrease was mainly attributed to ameliorations in socioeconomic conditions and living standards (Saavacool, 1986). Furthermore, the introduction of streptomycin, para-amino salicylic acid (PAS), and the availability of isoniazid marked the start of the contemporary period of effective treatment for the ailment in the mid-1940s. Subsequently, with the advent of 'short-course' treatment, the curative potential for tuberculosis was realized. Despite the continued widespread prevalence of tuberculosis in developing nations such as India during the late 1970s, a prevailing optimism existed within developed countries regarding the potential elimination of tuberculosis as a significant public health concern (Sharma SK, Mohan A, 2013).

The early 1980s witnessed a global resurgence of tuberculosis, primarily due to the emergence of Human Immunodeficiency Virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Several factors in low-income countries, including increased poverty, uncontrolled urbanization, and the destabilization of healthcare infrastructure and tuberculosis control programs, also contributed to the resurgence (Bloom, 1992; CDC, 1992; RossMan & MacGregor 1995). Furthermore, in the early 1990s, an outbreak of a drug-resistant tuberculosis strain in New York resulted in an 80% mortality rate among affected patients. The co-infection of HIV and tuberculosis, along with the spread of drug-resistant tuberculosis, severely aggravated the situation, prompting the World Health Organization (WHO) to declare tuberculosis a global emergency in 1993 (Natarajan A. *et al*., 2020).

The latter portion of the 1990's years was marked by the reemergence of drug-resistant tuberculosis (DR-TB), including rifampicin resistant TB (RR-TB) and multidrug-resistant tuberculosis (MDR-TB), characterized by resistance to Rifampicin and Isoniazid, which has presented a significant threat (Sharma SK, Mohan A., 2006; Central TB Division, 2012). The first decade of the 21st century has been ravaged by extensively drug-resistant TB (XDR-TB), defined as MDR-TB plus resistance to at least one drug from each of the two important classes of second-line agents, fluoroquinolones (levofloxacin or moxifloxacin) and injectables drugs namely amikacin, capreomycin or kanamycin (Dheda K *et al*., 2010; Sharma SK, Mohan A, 2013; Seung KJ *et al*., 2015). Recently, concern has been expressed regarding the occurrence of extremely drug-resistant TB (XXDR-TB), super XDR-TB, totally drug-resistant TB (TDR TB) from some parts of the world (Migliori GB *et al*., 2007; Velayati AA, Masjedi MR *et al*., 2009; Velayati AA, Farnia P. *et al*., 2009).

The WHO currently does not recognize the term "totally drug-resistant" for TB, as it lacks a clear definition. Consequently, such cases are classified as XDR-TB by the WHO, primarily due to the technical challenges and limitations associated with *in vitro* drug susceptibility testing (DST). A consensus on appropriate methods, critical drug concentrations for resistance definition, and the reliability and reproducibility of results for conventional DST has been established only for the drugs that define MDR-TB and XDR-TB (WHO, 2008a). The reproducibility and reliability of DST for other second-line drugs have not yet been established and require further correlation with clinical treatment responses. Therefore, the WHO advises against using these latter results to guide treatment decisions (WHO, 2008b).

In 2015, an estimated 10.4 million people developed TB, including 580.000 with MDR-TB or rifampicin-resistant TB (RR-TB), and 1.4 million died from the disease. However, it is noteworthy that despite these scenaries, approximately 6.1 million new tuberculosis cases were documented during that same period, indicating a substantial issue of underreporting (WHO, 2016). While an estimated 10.8 million individuals globally contracted tuberculosis in 2023, an increase from 10.7 million in 2022, the annual number of those developing multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) remained relatively stable between 2020 and 2023, following a gradual decline

from 2015 to 2020. In 2022, an estimated 410,000 individuals worldwide developed MDR/RR-TB. While the treatment success rate for those diagnosed with MDR/RR-TB has shown consistent improvement, it continues to be critically low. This rate reached 63%, an increase from 60% in 2019 and 50% in 2012 (WHO, 2024).

MDR/RR-TB continues to emerge and proliferate due to two primary factors: suboptimal management of tuberculosis treatment and direct interpersonal transmission. The majority of individuals afflicted with tuberculosis achieve remission through a six-month treatment regimen, provided with sufficient support. However, improper or erroneous administration of anti-tuberculosis medications, the utilization of inefficacious drug formulations (including monotherapy, substandard pharmaceuticals, or inadequate storage conditions), and premature cessation of treatment can induce drug resistance. This resistance subsequently facilitates transmission, particularly within densely populated environments such as correctional facilities and healthcare institutions. Patients suffering from pulmonary tuberculosis are capable of disseminating the disease via expectoration, sternutation, or mere vocalization. Infection can be acquired by inhaling a minimal quantity of these microorganisms (WHO, 2024).

Pharmacological Therapy

Comprehensive drug susceptibility testing is paramount to identify resistance to specific antitubercular medications, thereby guiding the choice of effective drugs. This is often complemented by an assessment of prior exposure to TB medicines, as previous treatment failures or incomplete courses can influence subsequent resistance patterns and the likelihood of successful treatment. A detailed patient history, encompassing comorbidities, allergies, and tolerance to various medications, is also crucial. Beyond the individual patient, the drug-resistance profile of close contacts can inform treatment decisions, particularly in cases where transmission within a household or community is suspected. This epidemiological link can help predict potential resistance patterns in the patient (WHO, 2024a).

Age plays a significant role, as certain drugs may have different safety or efficacy profiles in pediatric versus adult populations. The extent of pulmonary TB disease, including the presence of cavitation or extensive lung involvement, can influence the duration and intensity of treatment required. Furthermore, the localization of extrapulmonary TB lesions, such as those affecting the bones, joints, central nervous system, or lymph nodes, may necessitate specific drug penetration properties or longer treatment durations due to the inherent challenges in achieving therapeutic drug concentrations in these sites (Golden MP, Vikram HR, 2005; Moule MG, Cirillo JD, 2020; Vishnu Sharma M *et al*., 2022; WHO, 2024a).

The WHO's emphasis on individualized treatment underscores the complexity of managing MDR/RR-TB, highlighting the need for a comprehensive assessment of each patient's unique circumstances to optimize treatment outcomes and minimize the risk of further resistance development (WHO, 2024a).

For patients diagnosed with MDR/RR-TB who have no documented fluoroquinolone resistance and have not previously undergone second-line drug treatment, a 9-month all-oral regimen is recommended. This regimen includes bedaquiline (administered for six months) in conjunction with levofloxacin/moxifloxacin, ethionamide, ethambutol, high-dose isoniazid, pyrazinamide, and clofazimine. The latter six drugs are administered for an initial four months, with the potential for extension to six months if sputum smear positivity persists. This initial phase is succeeded by a five-month treatment period comprising levofloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide. Ethionamide may be substituted by a two-month course of linezolid (WHO, 2016a; WHO, 2024a). However, pregnancy was an exclusion criterion for the shorter MDR-TB treatment regimen studies. Two of the core components of the shorter MDR-TB regimens – the injectable agent and ethionamide (or prothionamide) – are usually contraindicated in pregnancy. Interrupting these medicines from the shorter MDR-TB treatment regimen could seriously compromise its effectiveness (WHO, 2016a). A 9-month regimen with linezolid instead of ethionamide shall be used in pregnant women, unlike the regimen with ethionamide (WHO, 2022).

Conversely, for patients diagnosed with MDR/RR-TB who do not meet the criteria for, or have not achieved a favorable therapeutic outcome from, the aforementioned 6-month or 9-month regimens, or whose TB disease is attributable to *M. tuberculosis* strains exhibiting XDR-TB, or who demonstrate intolerance to pivotal therapeutic components, extended individualized regimens represent viable treatment modalities for RR-TB or MDR-TB. These regimens typically extend over a duration of 18 months or more and may be either standardized or tailored, incorporating the pharmaceuticals listed in Chart 1. Such regimens are generally formulated to include a minimum complement requisite of second-line anti-tuberculosis agents, chosen based upon their presumed efficacy, which is inferred from the patient's medical history or drug-resistance profiles. For individuals afflicted with RR-TB or MDR-TB, a regimen encompassing at least five efficacious anti-TB drugs during the intensive phase is recommended (WHO, 2016a; WHO, 2024a).

This therapeutic approach mandates the inclusion of pyrazinamide and four critical second-line drugs: one from Group A, one from Group B, and a minimum of two from Group C. In instances where the prescribed minimum of effective drugs cannot be attained as delineated above, an agent from Group D2 and supplementary agents from Group D3 may be incorporated to achieve a total of five. Furthermore, for patients with RR-TB or MDR-TB, it is advised that the regimen be supplemented with high-dose isoniazid and/or ethambutol (WHO, 2016a; WHO, 2024a).

In 2022, the World Health Organization (WHO) issued a conditional recommendation for a 6-month treatment regimen consisting of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin (BPaLM) for patients diagnosed with multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB). This regimen is designated as the preferred option for the majority of patients afflicted with this condition. This recommendation prioritizes BPaLM over the previously employed 9-month or extended 18-month regimens. Drug susceptibility testing (DST) for fluoroquinolones is strongly advised for individuals with MDR/RR-TB. While the initiation of BPaLM should not be postponed pending DST results, these results should subsequently guide the decision regarding the retention or cessation of moxifloxacin from the regimen. In cases of confirmed fluoroquinolone resistance, BPaL (excluding moxifloxacin) should be commenced or maintained. However, this recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid (WHO, 2022; WHO, 2024a). Thus for pregnant women, it is recommended that a longer individualized regimen be used which can allow the inclusion of four or more effective second-line TB medicines with no known teratogenic properties.

Chart 1. Medicines recommended for the treatment of RR-TB and MDR-TB.

Groups		Drugs
Group A. Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin
Group B. Second-line injectable agents		Amikacin Capreomycin Canamycin (Streptomycin)*
Group C. Other core second-line agents		Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delaminid
	D3	*p*-aminosalicylic acid Imipenem–cilastatin Meropenem Amoxicillin-clavulanate

(Adapted from WHO, 2016a).

*For the treatment of RR-TB and MDR-TB, streptomycin is included as a substitute for second-line injectable agents when aminoglycosides or capreomycin cannot be used and susceptibility is highly likely. In the absence of susceptibility testing, streptomycin is not indicated.

CONCLUSION

In conclusion, the pharmacology of drugs used to treat resistant tuberculosis underscores the complexity of combating this challenging disease. Advances in drug development, such as second-line medications and novel therapeutic agents, have provided hope for treating multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. These efforts demand careful attention to drug efficacy, safety profiles, and optimal combination therapies to ensure successful outcomes while minimizing adverse effects. As resistance continues to evolve, it is imperative that ongoing research, global cooperation, and innovation pave the way for more effective, accessible, and sustainable solutions to combat tuberculosis resistance worldwide.

References

1. Savacool JW. Philadelphia and the White Plague. Trans Stud Coll Physicians Phila. 1986 Sep;8(3):147-81. PMID: 3532445
2. Bloom BR. Tuberculosis. Back to a frightening future. Nature. 1992 Aug 13;358(6387):538-9. doi: 10.1038/358538b0. PMID: 1501708.
3. CDC, Centers For Disease Control and Prevention. tuberculosis morbidity–united states, 1992. MMWR. Morbidity and mortality weekly report, v. 42, n. 36, p. 696- 697,703-704, 1993.
4. RossMan, M. d.; MacGregor, R. Introduction and brief history. 1. ed. philadelphia: McGraw-Hill, 1995.
5. Natarajan A, Beena PM, Devnikar AV, Mali S. A systemic review on tuberculosis. Indian J Tuberc. 2020 Jul;67(3):295-311. doi: 10.1016/j.ijtb.2020.02.005. Epub 2020 Feb 28. PMID: 32825856.
6. Sharma SK, Mohan A. Tuberculosis: From an incurable scourge to a curable disease - journey over a millennium. Indian J Med Res. 2013 Mar;137(3):455-93. PMID: 23640554; PMCID: PMC3705655.
7. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. Wkly Epidemiol Rec. 2006 Nov 10;81(45):430-2. English, French. PMID: 17096498.
8. Sharma SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest. 2006 Jul;130(1):261-72. doi: 10.1378/chest.130.1.261. PMID: 16840411.
9. Central TB Division. Revised National Tuberculosis Control 11. Programme. Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India. New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; 2012.
10. Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 14. years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat. Is "science" enough to tackle the epidemic?. Eur Respir J 2007; 29 : 423-7.
11. Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, 15. Ziazarifi AH, et al. Emergence of new forms of totally drug resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest 2009; 136 : 420-5.
12. Velayati AA, Farnia P, Masjedi MR, Ibrahim TA, Tabarsi P, 16. Haroun RZ, et al. Totally drug-resistant tuberculosis strains: evidence of adaptation at the cellular level. Eur Respir J 2009; 34 : 1202-3.
13. WHO, World Health Organization. Global tuberculosis report 2016. Geneva: WHO, 2016.
14. WHO, World Health Organization. Global tuberculosis report 2024. Genova: WHO, 2024.
15. Dheda K, Warren RM, Zumla A, Grobusch MP. Extensively drug-resistant tuberculosis: epidemiology and management challenges. Infect Dis Clin North Am. 2010 Sep;24(3):705-25. doi: 10.1016/j.idc.2010.05.001. PMID: 20674800.
16. Seung KJ, Keshavjee S, Rich ML. Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. Cold Spring Harb Perspect Med. 2015 Apr 27;5(9):a017863. doi: 10.1101/cshperspect.a017863. PMID: 25918181; PMCID: PMC4561400.
17. WHO (2008a) Policy guidance on drug susceptibility testing (DST) of second-line anti-tuberculosis drugs. http://whqlibdoc.who.int/hq/2008/WHO_ HTM_TB_2008.392_eng.pdf.
18. WHO (2008b) Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008. http://whqlibdoc.who.int/ publications/2008/9789241547581_eng.pdf.
19. WHO, World Health Organization. Tuberculosis: Multidrug-resistant (MDR-TB) or rifampicin-resistant TB (RR-TB). 2024a. https://www.who.int/news-room/questions-and-answers/item/tuberculosis-multidrug-resistant-tuberculosis-(mdr-tb)
20. WHO, World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. 2016a. https://www.who.int/publications/i/item/9789241549639
21. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician. 2005 Nov 1;72(9):1761-8. PMID: 16300038.
22. Moule MG, Cirillo JD. Mycobacterium tuberculosis Dissemination Plays a Critical Role in Pathogenesis. Front Cell Infect Microbiol. 2020 Feb 25;10:65. doi: 10.3389/fcimb.2020.00065. PMID: 32161724; PMCID: PMC7053427.
23. Vishnu Sharma M, Arora VK, Anupama N. Challenges in diagnosis and treatment of tuberculosis in elderly. Indian J Tuberc. 2022;69 Suppl 2:S205-S208. doi: 10.1016/j.ijtb.2022.10.001. Epub 2022 Oct 22. PMID: 36400510.
24. WHO, World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. https://www.who.int/publications/i/item/9789240063129