European Journal of Clinical and Biomedical Sciences
2025, Vol. 11, No. 1, pp. 11-15
https://doi.org/10.11648/j.ejcbs.20251101.12

Case Report

Emergence of Non-tuberculous Mycobacteria Infections in Patients with Drug-Resistant Tuberculosis (DR-TB) During Bedaquiline - Containing Treatment

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Abstract

Introduction: Environmental microorganisms known as non-tuberculous mycobacteria (NTM) are frequently found in soil and water, originating from both natural and man-made sources. All mycobacteria species are included in this group, with the exception of Mycobacterium leprae, which causes leprosy, and Mycobacterium tuberculosis complex, which causes tuberculosis. NTM consists of a diverse array of over 190 distinct species. Mycobacterium avium complex (MAC), which consists of Mycobacterium avium and Mycobacterium intracellulare, is the most common pathogen that causes disease in humans. Mycobacterium abscessus (MAB) is the next most common pathogen. *Methods:* The centre, Saint Peter's Specialized Hospital, is the pioneering TB specialized hospital in Ethiopia. Both conventional and molecular drug susceptibility testing were used to diagnose the patients with DR-TB. NTM-infected patients received therapy for their DR-TB using regimens containing bedaquiline, and they were monitored once treatment started. Sputum samples were gathered in order to evaluate the effectiveness of the treatment using mycobacterial culture. We have already come across two NTM cases. *Result:* Concerns have been raised about the occurrence of nontuberculous mycobacteria (NTM) infections in patients with drug-resistant tuberculosis (DR-TB) using bedaquiline-containing regimens. In a recent study, six cases of NTM infection were documented among patients undergoing treatment with Bedaquiline. The final treatment outcomes for these cases were cured. Bedaquiline is a prospective treatment option for NTM infections because it has shown excellent antibacterial action against a variety of NTM species. However, while effective against extra pulmonary NTM infections; its efficacy in pulmonary infections remains less clear. The increasing incidence of NTM infections in this patient population highlights the need for careful monitoring and potential adjustments in treatment strategies to address the complications arising from these co-infections. *Conclusion:* These outcomes underscore the complexity of managing co-infections in patients already burdened by DR-TB. It suggest that while Bedaquiline shows promise in treating DR-TB, its role in managing concurrent NTM infections requires careful consideration. The emergence of NTM during treatment may be influenced by factors such as the pharmacokinetics of Bedaquiline and the intrinsic resistance of various NTM species. This situation necessitates ongoing monitoring and potentially revised therapeutic strategies to address these co-infections effectively. As the incidence of NTM infections continues to rise globally, it is crucial for healthcare providers to remain vigilant in identifying and managing these infections in patients undergoing treatment for DR-TB.

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Received: 29 December 2024; **Accepted:** 13 January 2025; **Published:** 11 February 2025

Keywords

Non-tuberculous Mycobacteria, Drug-resistant Tuberculosis, Addis Ababa, Ethiopia

1. Introduction

Globally, tuberculosis (TB) continues to be the primary cause of mortality from infectious diseases [1]. The rise of drug-resistant TB significantly threatens global TB management and is a critical public health concern in numerous nations. The Global TB Report 2022 indicated that approximately 10.6 million individuals fell ill with TB that year [2, 3] In 2021, TB caused around 1.6 million deaths, including 1.4 million among HIV-negative persons and 187,000 among those with HIV. Additionally, in 2021, an expected 450,000 new cases of TB emerged, with 3.6% of new cases and 18% of previously treated patients being found to be multidrug-resistant or rifampicin-resistant [4, 5]. Drug-resistant tuberculosis (DR-TB) is difficult and complicated to treat. It involves the use of highly toxic anti-TB medications, which raises the risk of adverse effects, extends the duration of treatment, and incurs significant medical expenses [6]. As a result, only about half of the patients experience positive outcomes after receiving these treatments [7].

New anti-TB drugs that are efficient against Mycobacterium tuberculosis (MTB) must be developed immediately and operate through novel mechanisms of action [8]. Bedaquiline, a diarylquinoline, has been approved by the FDA for treating drug-resistant TB (DR-TB) [9]. As a promising new treatment for MTB, Bedaquiline shows potential for effectively addressing this challenging disease when properly optimized [10]. The World Health Organization endorses Bedaquiline for creating effective combination therapies against DR-TB [11], and its inclusion has shown significant efficacy in treating DR-TB patients [10, 12]. Through a nationwide trial program, Bedaquiline has been accessible to DR-TB patients in China since 2018 [13].

Environmental microorganisms known as non-tuberculous mycobacteria (NTM) are frequently found in soil and water, originating from both natural and man-made sources. All mycobacteria species are included in this group, with the exception of Mycobacterium leprae, which causes leprosy, and Mycobacterium tuberculosis complex, which causes tuberculosis. NTM consists of a diverse array of over 190 distinct species [14]. Mycobacterium avium complex (MAC), which consists of Mycobacterium avium and Mycobacterium intracellulare, is the most common pathogen that causes disease in humans. Mycobacterium abscessus (MAB) is the next most common pathogen [15].

Since non-tuberculous mycobacteria (NTM) infections are not considered notifiable diseases in many areas, it is challenging to collect reliable statistics on the prevalence. Over the previous ten years, the number of reported cases more than doubled in Queensland, Australia, where NTMs are notifiable, from 672 in 2012 to 1,490 in 2022 [16]. By 2040, NTM infections may triple, according to projections [17]. Mycobacterium tuberculosis isolates are currently eight times less common than NTM isolates; in 2023, 191 TB cases were reported, compared to 1,565 NTM isolates [18]. The clinical importance of NTM isolation and the choice to start treatment are more controversial, even if isolating M. tuberculosis suggests clinical disease. The ATS/IDSA guidelines help differentiate between NTM pulmonary disease and mere colonization based on clinical, microbiological, and radiological criteria [19].

Several theories have been proposed to explain the rising incidence of non-tuberculous mycobacteria (NTM) infections in recent years. Advances in diagnostic techniques have made it easier to accurately identify NTM infections, with faster and more specific tests available. Additionally, the number of immunocompromised individuals, who are more susceptible to NTM infections, is increasing. A survey by the National Health Insurance Service (NHIS) indicated a rise in immunocompromised individuals from 2.7% in 2013 to 6.6% in 2021 [20]. Furthermore, individuals with cystic fibrosis (CF), who are fortunately living longer, are also at a heightened risk for developing NTM infections [21].

Even though NTM infections are becoming more common, misdiagnosis is still a major problem. Clinically, nonspecific symptoms like fever, fatigue, weight loss, and persistent cough are seen with NTM infections [19]. Clinical symptoms, imaging demonstrating nodular or cavity opacities, and positive cultures from sputum, bronchial washings, or lung biopsies with mycobacterial histological characteristics are all necessary for the diagnosis, which also requires microbiological confirmation [19, 22]. Importantly, depending on the risk factors of each patient, a positive NTM isolation may not always mean an active infection or disease, making it more difficult to decide whether to start treatment or keep monitoring up.

Mycobacterium avium and other non-tuberculous mycobacteria (NTMs) are frequently encountered by the general public while they go about their daily lives. Showerheads are a frequent exposure source because they can aerosolize and inhale microorganisms from municipal water [22]. NTMs can also be present in soil during gardening and may be iso-

lated from hospital equipment [15].

1.1. Challenges of Current Treatment Options

Currently, at least three medications are used to treat non-tuberculous mycobacterial (NTM) infections. Most regimens consist of rifampicin and ethambutol in addition to a macrolide, such as azithromycin or clarithromycin [19]. However, research shows that within 6 to 12 months of completing initial medication, 10% to 60% of patients develop relapse or reinfection [23]. Antibiotic pharmacokinetic interactions could be one cause of these unfavorable results. Rifampicin dramatically lowered peak serum concentrations of macrolides, according to research by van Ingen et al., with levels of azithromycin and clarithromycin dropping by up to 23% and 68%, respectively [24]. Whether this drop in blood concentration has an impact on the macrolides' ability to eradicate lung bacteria is still unknown. Despite macrolides' high tissue penetration, the treatment regimen's overall efficacy may be lowered if these antibiotics don't work well together [25].

1.2. Determination of the Current Treatment Regimen

The first "American Thoracic Society (ATS) declaration for the identification and treatment of nontuberculous mycobacteria" was issued in 1990 and recommended a four-drug regimen. For the first two months of treatment, this regimen consisted of 300 mg of isoniazid, 600 mg of rifampin, and 25 mg/kg of ethambutol; for the remaining months, the dose reduced to 15 mg/kg. Furthermore, streptomycin recommended for the first three to six months of treatment [26].

Table 1. *Emergence of nontuberculous mycobacteria infections during anti-tuberculosis therapy, 2024.*

Sex	Age (years)	Patient Category	Drug Susceptibility	Comorbidity	Time of culture conversion	Time of NTM emergence	Treatment regimen	Outcome
F	30	Relapse	RR-PTB	NO	5th month	18th month	(All oral) longer regimen	cured
M	51	Relapse	MDR-PTB	NO	1st Month	6th month	BPaLM	Cured

2. Method

The center, Saint Peter's Specialized Hospital, is the pioneering TB specialized hospital in Ethiopia. Both conventional and molecular drug susceptibility testing were used to diagnose the patients with DR-TB. NTM-infected patients received therapy for their DR-TB using regimens containing bedaquiline, and they were monitored once treatment started. Sputum samples were gathered in order to evaluate the effectiveness of the treatment using mycobacterial culture. We have already come across two NTM cases. The period of time between the start of treatment and the negative sputum culture results was known as the "time to sputum culture conversion." Clinical and demographic data were gathered from medical records. The study received ethical approval from Saint Peter's Specialized Hospital's Institutional Review Board (IRB).

3. Results

The urgent need to create novel anti-TB drugs that are effective against Mycobacterium tuberculosis (MTB) and have a different mode of action [8]. The Food and Drug Administration has authorized bedaquiline, a drug belonging to the diarylquinoline class, for the treatment of DR-TB [9]. When properly optimized, bedaquiline, a new drug against MTB, has the potential to be used to fight this challenging disease [10]. The World Health Organization advises using bedaquiline to create combination regimens that effectively combat DR-TB [11]. Incorporating bedaquiline into the therapy of DR-TB patients has shown encouraging results [10, 12]. Since late 2016, DR-TB patients in Ethiopia have had clinical access to bedaquiline through a nationwide pilot program [13].

Concerns have been raised about the occurrence of nontuberculous mycobacteria (NTM) infections in patients with drug-resistant tuberculosis (DR-TB) using bedaquiline-containing regimens. In a recent study, two cases of NTM infection were documented among patients undergoing treatment with bedaquiline. The final treatment outcomes for these cases were cured. Bedaquiline is a prospective treatment option for NTM infections because it has shown excellent antibacterial action against a variety of NTM species. However, while effective against extra pulmonary NTM infections; its efficacy in pulmonary infections remains less clear. The increasing incidence of NTM infections in this patient population highlights the need for careful monitoring and potential adjustments in treatment strategies to address the complications arising from these co-infections.

4. Discussion

Concerns have been raised about the occurrence of nontuberculous mycobacteria (NTM) infections in patients with drug-resistant tuberculosis (DR-TB) using bedaquiline-containing regimens.

The increasing incidence of NTM infections in patients undergoing therapy for DR-TB may be attributed to several factors. First, while bedaquiline has shown promising antibacterial activity against various NTM species, its efficacy appears to be limited primarily to extra pulmonary infections rather than pulmonary ones. This limitation can complicate treatment strategies, especially in cases where patients present with both DR-TB and NTM infections.

Furthermore, the intrinsic resistance of many NTM species to standard antibiotics poses significant challenges. The presence of NTM infections during bedaquiline therapy may indicate a failure of the immune system to control these opportunistic pathogens, particularly in immunocompromised patients. Our findings align with previous studies that have reported high rates of relapse or reinfection in patients treated for NTM infections, highlighting the need for vigilant monitoring and potential adjustments in therapeutic approaches.

The emergence of NTM infections during bedaquiline therapy necessitates further research into optimal treatment regimens and the mechanisms underlying these co-infections. Understanding the pharmacokinetics and potential interactions between bedaquiline and other antimycobacterial agents is crucial in developing effective treatment strategies. Additionally, as the prevalence of NTM infections continues to rise globally, healthcare providers must remain vigilant in recognizing and managing these infections in patients undergoing treatment for DR-TB.

5. Conclusion and Recommendations

Concerns have been raised about the occurrence of nontuberculous mycobacteria (NTM) infections in patients with drug-resistant tuberculosis (DR-TB) using bedaquiline-containing regimens. In our case study, we documented two instances of NTM infections, with both patients achieving cure. The findings suggest that while bedaquiline shows promise in treating DR-TB, its role in managing concurrent NTM infections requires careful consideration. The emergence of NTM during treatment may be influenced by factors such as the pharmacokinetics of bedaquiline and the intrinsic resistance of various NTM species. This situation necessitates ongoing monitoring and potentially revised therapeutic strategies to address these co-infections effectively.

As the incidence of NTM infections continues to rise globally, it is crucial for healthcare providers to remain vigilant in identifying and managing these infections in patients undergoing treatment for DR-TB. Future research should focus on optimizing treatment regimens that incorporate bedaquiline while addressing the challenges posed by NTM, ultimately aiming to improve patient outcomes in this vulnerable population.

Abbreviation

BPaLM	Bedaquiline, Pretomanid, Linezolid and Moxifloxacin
CF	Cystic Fibrosis
DR-TB	Drug- resistant Tuberculosis
NHIS	National Health Insurance Service
MAB	Mycobacterium Abscessus
MAC	Mycobacterium Avium Complex
NTM	Non-tuberculous Mycobacteria
TB	Tuberculosis

Acknowledgments

We would like to thank all multidrug resistance patient treatment team who are participated in the care of the patients.

Authors' Contribution

Mustofa Hassen Yesuf: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing

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Each author certifies that they fulfill the most recent ICMJE Authorship requirements.

Ethical Approval and Informed Consent

All patients gave their informed consent before the study was published. The study received ethical approval from Saint Peter's Specialized Hospital's Institutional Review Board (IRB).

Data Avaiablity Statement

The data are available with corresponding author upon reasonable request will provide.

Funding

No grant from a public, private or nonprofit organization.

Conflicts of Interest

The authors state that none of the work described in this study could have been influenced by any known competing financial interests or personal relationships.

References

[1] Muttarak M, ChiangMai W, Lojanapiwat B. Tuberculosis of the genitourinary tract: imaging features with pathological correlation. Singapore medical journal. 2005; 46(10): 568.

[2] Migliori GB, Dheda K, Centis R, Mwaba P, Bates M, O'Grady J, et al. Review of multidrug-resistant and extensively drug-resistant TB: global perspectives with a focus on sub-Saharan Africa. Tropical Medicine & International Health. 2010; 15(9): 1052-66.

[3] Organization WH. WHO country stories: delivering for all: World Health Organization; 2023.

[4] Organization WH. Contributions of WHO to South Africa's health agenda: evaluation of the Country Cooperation Strategy 2016-2020. 2022.

[5] Seid MA, Ayalew MB, Muche EA, Gebreyohannes EA, Abegaz TM. Drug-susceptible tuberculosis treatment success and associated factors in Ethiopia from 2005 to 2017: a systematic review and meta-analysis. BMJ open. 2018; 8(9): e022111.

[6] Xu LD, Xu EL, Li L. Industry 4.0: state of the art and future trends. International journal of production research. 2018; 56(8): 2941-62.

[7] WHO GS. Global status report on noncommunicable diseases 2010. 2014.

[8] Campani φ A, Moreira R, Lopes F. Drug discovery in tuberculosis. New drug targets and antimycobacterial agents. European journal of medicinal chemistry. 2018; 150: 525-45.

[9] Mahajan S. Critique of mechanisms of formation of deformation, annealing and growth twins: Face-centered cubic metals and alloys. Scripta Materialia. 2013; 68(2): 95-9.

[10] Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. International journal of infectious diseases. 2020; 92: 214-7.

[11] Organization WH. WHO global report on traditional and complementary medicine 2019: World Health Organization; 2019.

[12] Mbuagbaw L, Guglielmetti L, Hewison C, Bakare N, Bastard M, Caumes E, et al. Outcomes of bedaquiline treatment in patients with multidrug-resistant tuberculosis. Emerging infectious diseases. 2019; 25(5): 936.

[13] Mpobela Agnarson A, Williams A, Kambili C, Mattson G, Metz L. The cost-effectiveness of a bedaquiline-containing short-course regimen for the treatment of multidrug-resistant tuberculosis in South Africa. Expert Review of Anti-infective Therapy. 2020; 18(5): 475-83.

[14] Armstrong DG, Tan T-W, Boulton AJ, Bus SA. Diabetic foot ulcers: a review. Jama. 2023; 330(1): 62-75.

[15] Falkinham III JO, editor Ecology of nontuberculous mycobacteria—where do human infections come from? Seminars in respiratory and critical care medicine; 2013: Thieme Medical Publishers.

[16] De Souza JC, Letson HL, Gibbs CR, Dobson GP. The burden of head trauma in rural and remote North Queensland, Australia. Injury. 2024; 55(3): 111181.

[17] Ratnatunga CN, Lutzky VP, Kupz A, Doolan DL, Reid DW, Field M, et al. The rise of non-tuberculosis mycobacterial lung disease. Frontiers in immunology. 2020; 11: 303.

[18] Gavaghan B, Finch J, Clarke K. Creating a framework for change: transitioning to value-based healthcare in Queensland. Australian Health Review. 2024; 48(2): 123-8.

[19] Griffith DM, Mason M, Yonas M, Eng E, Jeffries V, Plihcik S, Parks B. Dismantling institutional racism: theory and action. American journal of community psychology. 2007; 39: 381-92.

[20] Martinson ML, Lapham J. Prevalence of immunosuppression among US adults. JAMA. 2024.

[21] Ruseckaite R, Salimi F, Earnest A, Bell SC, Douglas T, Frayman K, et al. Survival of people with cystic fibrosis in Australia. Scientific Reports. 2022; 12(1): 19748.

[22] Gebert LF, MacRae IJ. Regulation of microRNA function in animals. Nature reviews Molecular cell biology. 2019; 20(1): 21-37.

[23] Lee I, Lee K. The Internet of Things (IoT): Applications, investments, and challenges for enterprises. Business horizons. 2015; 58(4): 431-40.

[24] van Ingen J, Boeree MJ, van Soolingen D, Mouton JW. Resistance mechanisms and drug susceptibility testing of nontuberculous mycobacteria. Drug Resistance Updates. 2012; 15(3): 149-61.

[25] Zuckerman B, Rhee JH, Song I, Bessell M. The Tucana/Horologium, Columba, AB Doradus, and Argus associations: new members and dusty debris disks. The Astrophysical Journal. 2011; 732(2): 61.

[26] Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis & Rheumatism. 1990; 33(8): 1101-7.