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A Case Series of Extensively Drug-Resistant Tuberculosis: Treatment Response and Risk Factor Profile from a Tertiary Care Center in Karachi

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ABSTRACT

Background: Tuberculosis is a growing public health concern in Pakistan. The increasing burden of drug-resistant TB poses a major threat nationwide. Lack of awareness, demographic factors, illiteracy, and inadequate healthcare facilities contribute significantly to its spread.

Objective: To evaluate the outcome of treated extensively drug-resistant tuberculosis (XDR-TB) patients registered at the Odisha Institute of Chest Diseases (OICD), a tertiary care hospital.

Methodology: This is a retrospective case-series study conducted on patients registered for extensively drug-resistant tuberculosis (XDR-TB) treatment from January 2017 to January 2021. All data was extracted on Excel sheets. Appropriate statistical methods were employed using Statistical Package for Social Sciences (SPSS) to analyze the frequencies and percentages.

Results: In the present case series, 5 patients were included according to the criteria for XDR-TB patients, of whom 3 were male and 2 were female. Treatment lasted for 24 months; 4 were declared completed upon showing sputum conversion, while 1 was declared dead. No adverse effects were observed.

Conclusion: In conclusion, the management of drug-resistant tuberculosis poses significant challenges, highlighting the vital importance of tailored treatment strategies and vigilant surveillance. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains necessitates innovative approaches, such as the utilization of second-line medications like bedaquiline and delamanid, in order to achieve successful outcomes

Keywords: Tuberculosis (TB); Multidrug-Resistant Tuberculosis (MDR-TB); Extensively Drug-Resistant Tuberculosis (XDR-TB)

Introduction

Tuberculosis (TB) is a chronic communicable disease that is one of the major global health concerns. Approximately one-third of the world's population is infected with Mycobacterium Tuberculosis.[1] It is an Infectious disease that is spread through respiratory droplets.

Pakistan carries a high burden of both drug-sensitive and drug-resistant TB. According to the World Health Organization (WHO) report, Pakistan accounts for about 510,000 new TB cases each year.[1,2] It is a significant issue for Pakistan, which has a total population of 231.4 million and is currently ranked fifth on the list of countries with the highest TB prevalence according to the WHO global TB report 2024. Within Pakistan, Karachi, a densely populated city, faces unique challenges in TB control, including overcrowding, limited healthcare access, and a large private sector that may contribute to irregular treatment practices. These conditions can foster the development and transmission of drug-resistant strains. While the national TB program has scaled up efforts to diagnose and manage multidrug-resistant TB (MDR-TB), data on the treatment outcomes and specific risk profiles of patients with XDR-TB in public sector facilities in Karachi remain limited.

Despite TB being a treatable disease, millions of people succumb to it, leading to a need for developing new treatment regimens to combat the disease. Since the emergence of medication, the burden of drug-resistant tuberculosis has increased considerably and poses a major public health concern. Extensively drug-resistant TB (XDR) strains are defined as multidrug-resistant TB strains that are resistant to at least one and that are also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other Group A drug (bedaquiline or linezolid).[3] It is estimated that 9.6% of the multidrug-resistant (MDR-TB) cases worldwide have XDR-TB.[3,4]

Existing literature from high-burden settings identifies several risk factors for the development of XDR-TB and poor outcomes. These include previous TB treatment failures, inadequate initial regimens, comorbidities such as diabetes mellitus, and socioeconomic factors, such as low education and income.[5,6] The specific applicability of these factors in Karachi's public health context, however, requires further investigation.

To effectively reduce the burden of Tuberculosis, it is necessary to conduct a thorough study to identify the risk factors that contribute to the development of extensively drug-resistant tuberculosis among individuals and their outcomes. Our case series is concerned with monitoring 5 XDR patients over a 2-year period while administering combination chemotherapy, including drugs like Moxifloxacin (MFX), ETO (ethionamide), BDQ (Bedaquilline), cycloserine (CS), and para-aminosalicylic acid (PAS), and to evaluate their clinical outcomes and ultimately enhance the management of extensively drug-resistant TB.

This study presents a detailed case series of five XDR-TB patients treated at a public tertiary care hospital in Karachi, describing their clinical presentation, treatment regimens, outcomes, and risk profiles. We aim to add a local perspective on XDR-TB management and highlight challenges and opportunities for improving care in similar resource-limited settings.

Objective

To monitor and evaluate the outcome of treated XDR-TB patients registered at OICD, a tertiary care hospital.

Methodology

A retrospective case series was conducted at the Ojha Institute of Chest Diseases (OICD), Dow University of Health Sciences, Karachi. Established in 1939 as a TB sanatorium, OICD was upgraded to an institute in 1975. The 350-bed hospital is a designated facility for managing drug-resistant tuberculosis under the National Tuberculosis Control Program.

The study included all adult patients (aged 15 years and above, including pregnant patients) with a confirmed diagnosis of XDR-TB who were registered at OICD between January 2017 and January 2021. The study was restricted to patients who were treatment-naive for XDR-TB regimens. Patients not registered at the facility, as well as those with drug-sensitive TB, mono-drug-resistant TB, or Rifampicin-resistant (R/R) TB, were excluded.

Following registration, all patients underwent a comprehensive baseline assessment. This included a physical examination with vitals and a series of diagnostic evaluations. The diagnostic workup consisted of sputum tests (GeneXpert, Xpert XDR, and culture with drug susceptibility testing), Chest X-rays, and baseline laboratory investigations. These investigations comprised complete blood counts (CBC), renal and liver function tests, serum electrolyte analysis, thyroid function tests, and electrocardiogram (ECG) assessments. Patient weight and height were also recorded.

A physician reviewed all test results and, where necessary, arranged a cardiac consultation to determine the most appropriate individualized treatment regimen. After providing verbal and written informed consent, each patient commenced a treatment course of 22 to 24 months.

Patients were scheduled for monthly follow-up visits. During these visits, clinical assessments, including temperature and weight measurements, were performed. Sputum samples were also collected to monitor culture conversion throughout the treatment period. Any adverse effects related to the treatment were documented and managed concurrently.

Operational Definitions

Drug-Susceptible Tuberculosis (DS-TB)
Tuberculosis caused by strains of Mycobacterium tuberculosis that remain sensitive to all first-line anti-TB drugs, including isoniazid, rifampicin, ethambutol, and pyrazinamide, ensuring full efficacy of standard treatment regimens.

Mono-Drug-Resistant Tuberculosis
TB caused by strains resistant to a single first-line anti-TB drug.

Rifampicin-Resistant Tuberculosis (RR-TB)
Tuberculosis caused by strains of Mycobacterium tuberculosis that exhibit resistance to rifampicin, with or without accompanying resistance to other first-line anti-TB drugs such as isoniazid, ethambutol, or pyrazinamide.

Multidrug-Resistant Tuberculosis (MDR-TB)
Mycobacterium tuberculosis strain causing TB that is resistant to at least both isoniazid and rifampicin, which are considered the two most potent first-line anti-tuberculosis (anti-TB) drugs.

Extensively Drug-Resistant Tuberculosis (XDR-TB)
Extensively drug-resistant TB (XDR) strains are defined as multidrug-resistant TB strains that are resistant to at least one Group A drug (bedaquiline or linezolid) and at least one fluoroquinolone (levofloxacin or moxifloxacin), in addition to being resistant to at least isoniazid and rifampicin.

GeneXpert
A rapid molecular test endorsed by WHO that detects Mycobacterium tuberculosis complex DNA and resistance to rifampicin by identifying mutations in the rpoB gene.

Xpert XDR
An advanced molecular test designed to detect resistance to additional TB drugs beyond rifampicin, facilitating the identification of XDR-TB cases.

Drug Susceptibility Testing (DST)
Laboratory testing to determine the susceptibility of Mycobacterium tuberculosis strains to anti-tuberculosis (anti-TB) drugs, guiding the development of effective treatment regimens.

Short-Term Treatment Regimen (STR)
A treatment approach designed to cure MDR-TB in a shorter duration (typically 9–12 months) compared to conventional longer treatment regimens.

Cured
The patient has at least three consecutive negative sputum cultures collected at least 30 days apart in the final 12 months of treatment.

Results

Five patients were included in this retrospective case series. None underwent treatment for extensively drug-resistant tuberculosis (XDR-TB). All followed a regular treatment regimen known as Modified LTR and showed resistance to HRZE, FQ, KM, and AM. Three patients (60%) were male, and two (40%) were female. All tested negative for HIV. Three (60%) were newly registered, while two (40%) had previously undergone treatment at OICD. All tested positive for sputum before treatment. The treatment lasted 24 months. Four patients were reported as cured with sputum conversion; one death occurred. Two patients (40%) had bilateral lung involvement, and three (60%) had unilateral lung involvement. The mean age was 33.8 years, and the mean starting weight was 46 kg. No comorbid conditions were observed. This is demonstrated in Table 1.

Discussion

Mycobacterium Tuberculosis can develop resistance to drugs through single-point mutations in its genome, making it more susceptible to resistance.5 The incomplete treatment of tuberculosis, combined with an increased susceptibility to mutations, can lead to the development of drug-resistant strains of the disease.5 MDR-TB is defined as resistance to isoniazid and rifampin.

In this study, we observed that four patients had a successful treatment outcome using the modified LTR regimen at OICD. Two of these patients had previously been treated with first-line drugs at OICD. After completing a 6-month treatment, positive culture and gene Xpert tests indicated rifampin resistance. Drug susceptibility testing (DST) revealed resistance to first-line drugs HREZ and second-line drugs KM+AM+CM. This led to treatment failure. The patients were then switched to second-line drugs (SLD). One patient was treated with regimen Z, AM, LFX, ETO, CS, and B6, while the other patient was given CM, LFX, ETO, CS, Z, PAS, AUG, KLR, LNZ, and INH. Unfortunately, treatment failure was observed with SLD. Out of the 2 patients, one was cured who was given 12CM,Z,MFX,ETO,CS,B6,PAS, LNZ,BDQ(6),CFZ/12,Z,MFX,ETO,CS,B6,,PAS,LNZ,CFZ, but the other patient who was administered 12CM,Z,MFX,ETO,CS,BDQ(6) PAS, AUG, KLR, LNZ, INH, B6,/ 12,Z,MFX,ETO,CS,B6, PAS, AUG, KLR, LNZ, INH, died due to an extensive nature of disease.

Table 1. Summary of Cases

S. No	Age, /Gender	Starting Weight(kgs)	Comorbid Disease/Complications	Lung involvement	Failing Regimen	Added Drugs	Treatment Outcome
1	26, Male	46	None	Unilateral	Z,AM,LFX,ETO,CS,B6	12CM,Z,MFX,ETO,CS,B6,PAS,LNZ,BDQ(6),CFZ/12,Z,MFX,ETO,CS,B6,,PAS,LNZ,CFZ	Cured
2	24, Male	37	None	Unilateral	CM, LFX, ETO,CS, Z,PAS AUG, KLR, LNZ, INH	12CM,Z,MFX,ETO,CS,BDQ(6) PAS, AUG, KLR, LNZ, INH, B6,/12,Z,MFX,ETO,CS,B6, PAS, AUG, KLR, LNZ, INH,	Died
3	27, Male	44	None	Unilateral	Not known	12CM,Z,MFX,ETO,CFZ, LNZ,BDQ,CS,B6/12 Z,MFX,ETO,CFZ,LNZ,BDQ,CS,B6	Cured
4	60, Male	61	None	Unilateral	Not known	12AM,Z,LNZ,MFX,ETO, CS,CFZ,B6/12 Z,LNZ,MFX,ETO,CS,CFZ,B6	Cured
5	32, Male	42	None	Unilateral	Not known	20BDQ,DLM,LNZ,CFZ, CS,ETO,PAS,Z	Cured

During outpatient clinics, three unregistered patients were observed. These patients had taken the primary TB regimen, but it is uncertain whether they were adherent to it. Tests, including Gene Xpert, DST, and Culture, were conducted. Two patients tested positive for culture, with Gene Xpert indicating rifampin resistance and DST showing positivity for HREZ, KM+AM+CM. A 27-year-old male was treated with a regimen consisting of CM, Z, MFX, ETO, CFZ, LNZ, BDQ, CS, and B6/12, and the patient was successfully cured. A 60-year-old female was treated with a regimen consisting of AM, Z, LNZ, MFX, ETO, CS, CFZ, and B6/12, resulting in successful treatment and cure. Lastly, one patient had a positive culture and a positive Gene Xpert result for rifampin resistance, and Line Probe Assay (LPA) testing was performed, which revealed resistance to HR, FQ, and SLI. This patient received a treatment consisting of 20 BDQ, DLM, LNZ, CFZ, CS, ETO, PAS, and Z, and was successfully cured.

Isoniazid is one of the first-line drugs used for the treatment of TB. It has a bacteriostatic effect in the first 24 hours, followed by bactericidal effects. Isoniazid (INH) works by inhibiting the synthesis of mycolic acid, destroying the mycobacterial cell wall. Its primary targets are the InhA and KasA proteins.[7] NH also interferes with protein, lipid, and carbohydrate synthesis, as well as NAD metabolism. Activation by the KatG enzyme is necessary for its effectiveness. Resistance of MTB to INH is associated with the loss of "P" and "C" activities.[8] Fluoroquinolones work by binding to bacterial enzymes, inhibiting DNA replication and transcription.[8] Fourth-generation fluoroquinolones bind to both enzymes, making it harder for bacteria to develop resistance. Moxifloxacin, GTX, and Levofloxacin are potent FDA-approved drugs used to treat TB. BDQ targets mycobacterial ATP synthase, the enzyme supplying energy to Mycobacterium Tuberculosis.[9] It exhibits a strong bactericidal and sterilizing action against Mycobacterium tuberculosis (M. tuberculosis) in laboratory studies. The WHO recommends BDQ for MDR-TB if the organism is resistant to other second-line drugs, if the patient cannot tolerate second-line drugs, or if alternative drugs are unavailable. Resistance to BDQ is believed to be caused by mutations in the Rv0678 gene, which encodes an efflux pump.[4,10]

The prevalence of drug-resistant TB poses a significant public health challenge in endemic countries such as Pakistan. Our research findings indicate that 80% of

patients with extensively drug-resistant tuberculosis treated at a government hospital achieved successful outcomes. This success rate is markedly higher than the national average of 40.6% and the global average of 39%.[11,12] One potential explanation for this elevated success rate could be the absence of HIV as a comorbid condition in the patients. Furthermore, a study conducted in Germany also revealed that in the absence of HIV, treatment success rates ranged from 80-89%.[10] The increased recovery rate among the patients can be attributed to their young age at the time of treatment. As the majority of individuals were diagnosed and treated at a young age, they did not have significant other health conditions, thereby facilitating more manageable treatment.

The study suggests that patients with lower starting weights may be more likely to benefit from TB treatments. This correlation may be due to undernourishment and poorer health, which could lead to more complications during treatment and worse outcomes. It's important to note that undernutrition or malnutrition has been identified as a risk factor for poor outcomes in XDR TB.[13] A study conducted in South Africa in 2016 on patients with extensively drug-resistant TB showed that a weight < 50kgs at the time of initiation of treatment was considered the strongest predictor of unfavorable outcomes.[14]

Our research has been instrumental in assessing the risk factors and clinical outcomes of patients with extensively drug-resistant TB at one of the largest public sector hospitals in the country. However, it is important to note that our study was limited by a relatively small sample size. It is crucial to conduct further evaluations on a larger group of patients undergoing this treatment to obtain a more comprehensive understanding of treatment outcomes and potential side effects.

Conclusion

In conclusion, the management of drug-resistant tuberculosis poses significant challenges, highlighting the vital importance of tailored treatment strategies and vigilant surveillance. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains necessitates innovative approaches, such as the utilization of second-line medications like bedaquiline and delamanid, in order to achieve successful outcomes. Our study underscores the varying success rates in different clinical settings, influenced by factors such as patient age, nutritional status, and the presence of comorbidities like HIV. Addressing these complexities calls for a multidisciplinary approach that integrates robust public health measures with advances in diagnostic and therapeutic interventions. Continued research and international collaboration are essential for enhancing treatment efficacy, mitigating the development of resistance, and ultimately reducing the global burden of tuberculosis.

Ethical Approval

The ethical approval was obtained from the Institutional Review Board with Ref: IRB-3184/DUHS/Approval/2023. Verbal as well as a written consent is taken from the patients arriving at the outpatient department, patient anonymity is well maintained.

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