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Recurrent drug-resistant pulmonary tuberculosis with fibrocavitatory lung disease: A case series from a tertiary tuberculosis centre in Mumbai, India

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Abstract
Background: Drug-resistant tuberculosis (DR-TB) remains a major challenge in tuberculosis control, particularly among patients with recurrent disease and structural lung damage.
Objective: To describe the clinical presentation, resistance patterns, and management of recurrent rifampicin-resistant pulmonary tuberculosis in three patients treated at a tertiary TB center.
Methods: A retrospective case series of three adult male patients with microbiologically confirmed rifampicin-resistant tuberculosis admitted at a tertiary tuberculosis hospital in Mumbai. Clinical, radiological, and molecular diagnostic findings were analyzed along with treatment strategies under the National TB Elimination Programme.
Results: All three patients presented with chronic respiratory symptoms and prior tuberculosis history. Molecular testing confirmed rifampicin resistance in all cases, with two patients demonstrating additional fluoroquinolone resistance suggestive of Pre-XDR tuberculosis. Radiological findings showed fibrocavitatory lung disease and extensive structural damage. Individualized all-oral regimens including Bedaquiline, Linezolid, Delamanid, Cycloserine, and Clofazimine were initiated according to resistance profiles.
Conclusion: Recurrent tuberculosis with drug resistance represents a complex clinical challenge requiring rapid molecular diagnosis and individualized treatment regimens. Comprehensive management including control of comorbidities and addiction is essential to improve outcomes and prevent transmission.

Keywords: Drug-resistant tuberculosis, Pre-XDR TB, recurrent tuberculosis, Bedaquiline, fibrocavitatory disease

Introduction
Tuberculosis (TB) continues to be a major public health challenge globally and in India. Despite effective chemotherapy, recurrence and emergence of drug-resistant tuberculosis (DR-TB) remain significant obstacles to TB elimination. Recurrent TB may occur due to relapse of the same strain or reinfection with a new strain, both of which are increasingly associated with drug resistance [1]. Rifampicin-resistant TB (RR-TB) and Pre-XDR TB (RR-TB with fluoroquinolone resistance) are associated with prolonged infectivity, high mortality, economic burden, and social stigma [2]. Patients with previous TB, structural lung disease, addictions, and comorbidities such as diabetes are at higher risk of recurrence and progression to DR-TB [3]. Early molecular diagnosis and individualized all-oral regimens under NTEP have improved outcomes, yet recurrent DR-TB continues to be reported in tertiary care settings.

Overview & Background
Drug resistance in TB arises due to a complex interaction between bacillary factors (genetic mutations), host factors (immune dysfunction, comorbidities), pharmacological factors (subtherapeutic drug levels), and health system issues (treatment interruption, delayed diagnosis) [4]. Recurrent pulmonary TB often leads to fibrocavitatory lung disease, which creates niches for bacillary persistence and drug resistance amplification [5]. With the transition to injectable-free regimens using newer drugs like Bedaquiline and Delamanid, treatment success rates have improved; however, individualized regimens are required for Pre-XDR and XDR TB based on molecular resistance patterns [6]. The burden of DR-TB in urban India is compounded by overcrowding, migration, poverty, addiction, and poor nutrition [7].

Historical Background
The evolution of TB management from sanatorium-based care to DOTS and now to precision medicine has transformed patient outcomes. The DOTS strategy reduced TB mortality significantly; however, programmatic gaps and inconsistent adherence led to the emergence of MDR-TB [8]. The introduction of molecular diagnostics (Xpert MTB/RIF, Line Probe Assays) revolutionized early detection of drug resistance [9]. More recently, WHO and NTEP have endorsed all-oral regimens containing Bedaquiline, Linezolid, and Delamanid, replacing toxic injectable agents and improving survival [6,10]. Despite these advances, recurrent DR-TB remains a challenge in patients with prior TB and poor social determinants of health.

Epidemiology
Globally, TB causes over 10 million new cases annually, with India contributing approximately 26–28% of the global burden [1]. Drug-resistant TB constitutes 3–4% of new TB cases and up to 18–25% of previously treated cases in India [2]. Urban slums, prisons, migrant populations, and individuals with alcohol use disorder and diabetes have

disproportionately higher rates of DR-TB [3,7]. Reinfection with resistant strains is increasingly reported in high-burden settings, highlighting ongoing community transmission [11]. Mumbai remains one of the high DR-TB burden cities in India, with a substantial proportion of Pre-XDR TB cases reported from tertiary care hospitals [12].

Pathology

Pulmonary TB is characterized by granulomatous inflammation with central caseation necrosis. Progressive disease leads to cavitation, fibrosis, bronchiectasis, and destruction of lung parenchyma [13]. Fibrocavitatory lesions harbor large bacillary loads and provide hypoxic, acidic microenvironments where drug penetration is poor, allowing bacilli to persist and develop resistance [14]. Repeated episodes of TB result in permanent structural damage, serving as reservoirs for persistent bacilli and recurrent infection.

Pathophysiology & Pathogenesis

Mycobacterium tuberculosis survives within macrophages and necrotic lesions by evading host immune responses and entering dormant "persister" states [15]. Drug resistance arises due to spontaneous chromosomal mutations (e.g., *rpoB*, *katG*, *gyrA*) selected under suboptimal drug exposure [16]. Structural lung disease reduces drug delivery to infected sites, while comorbid diabetes and alcoholism impair cellular immunity and macrophage function [3, 17]. Treatment interruption, malabsorption, and pharmacogenomic variability further reduce effective drug concentrations, promoting selection of resistant strains and recurrence [18]. Reinfection with resistant strains also contributes to recurrence in high-transmission settings [11].

Clinical Features (C/F) & Differential Diagnosis (DD)

Clinical Features

- Chronic cough with expectoration
- Fever and constitutional symptoms
- Progressive breathlessness
- Weight loss and fatigue
- Radiological fibrocavitatory disease
- History of previous TB and repeated admissions

Differential Diagnosis

- Chronic pulmonary aspergillosis
- Post-TB bronchiectasis with secondary infection
- Lung carcinoma
- Non-tuberculous mycobacterial disease
- Interstitial lung disease with superadded infection [19]

Academic Discussion

Recurrent DR-TB represents a failure of sterilizing cure and ongoing transmission. Fibrocavitatory disease increases bacillary burden and decreases drug penetration, facilitating resistance amplification [14]. Molecular diagnostics enable early detection of resistance and prevent inappropriate use of first-line regimens [9]. All-oral regimens improve adherence and reduce toxicity; however, Pre-XDR TB requires individualized regimens with careful monitoring for QT prolongation, cytopenias, and neuropathy [6]. Integration of TB care with addiction services, diabetes management, nutritional support, and psychosocial counseling is essential for sustained cure [3,7]. Programmatic strengthening and community-based adherence support remain key to TB elimination.

Methods

Study Design and Setting

This study is a retrospective descriptive case series conducted at the Group of Tuberculosis Hospitals, Sewri, Mumbai, a tertiary referral center for drug-resistant tuberculosis (DR-TB) under the National TB Elimination Programme (NTEP). The hospital manages complicated pulmonary and extrapulmonary TB cases referred from multiple public and private healthcare facilities in Mumbai and surrounding regions.

Study Population

Three adult male patients admitted with suspected recurrent pulmonary tuberculosis and subsequently confirmed as rifampicin-resistant tuberculosis (RR-TB) were included in this case series. These patients presented with chronic respiratory symptoms and had a previous history of tuberculosis treatment.

Inclusion Criteria

Patients were included if they fulfilled the following criteria:

1. Age ≥18 years
2. Clinical features suggestive of pulmonary tuberculosis
3. History of previous TB treatment
4. Microbiological confirmation of *Mycobacterium tuberculosis* with rifampicin resistance detected on Xpert MTB/RIF assay
5. Managed with all-oral longer regimen under NTEP

Clinical Evaluation

All patients underwent a detailed clinical assessment including:

- History of prior tuberculosis and treatment details
- Evaluation of comorbid conditions (diabetes, hypertension)
- Assessment of addiction history (alcohol, smoking, cannabis)
- Physical examination and evaluation of respiratory symptoms

Diagnostic Investigations

Microbiological Diagnosis

- **Sputum Xpert MTB/RIF:** assay was used for rapid detection of *Mycobacterium tuberculosis* and rifampicin resistance.

- **Line Probe Assay (LPA):** was performed for detection of resistance to first-line drugs (isoniazid) and second-line drugs (fluoroquinolones).

Radiological Assessment

Chest radiography was performed in all patients to assess:

- Cavitary lesions
- Fibrotic lung changes
- Bilateral pulmonary involvement

Baseline Laboratory Evaluation

Prior to initiation of DR-TB treatment, baseline investigations included:

- Complete blood count
- Liver function tests
- Renal function tests
- Electrocardiogram (ECG) for QT interval monitoring

Treatment Protocol

All patients were initiated on individualized all-oral longer regimens as per NTEP guidelines. The regimens included combinations of:

- Bedaquiline (BDQ)
- Linezolid (LNZ)
- Delamanid (DLM) (in selected cases)
- Levofloxacin or alternative drugs based on resistance profile
- Cycloserine
- Clofazimine

All patients received pyridoxine supplementation to prevent neurotoxicity associated with cycloserine.

Monitoring and Follow-up

Patients were monitored for:

- Clinical response
- Drug adverse effects
- ECG changes (QT prolongation)
- Hematological toxicity associated with Linezolid

Treatment decisions were individualized based on drug resistance patterns, clinical condition, and comorbidities.

Results

Patient Characteristics

The case series included three adult male patients aged 34, 48, and 65 years who presented with symptoms of recurrent pulmonary tuberculosis. All patients reported chronic cough, fever, breathlessness on exertion, and generalized weakness. Each patient had a history of previous tuberculosis treatment, suggesting possible relapse or reinfection.

Two patients had significant addiction history, including alcohol use and smoking, while one patient had multiple comorbidities including diabetes mellitus and hypertension.

Microbiological Findings

All three patients were confirmed to have rifampicin-resistant tuberculosis on Xpert MTB/RIF assay.

Further molecular testing using Line Probe Assay (LPA) revealed varying resistance patterns:

- **Case 1:** Rifampicin resistance detected
- **Case 2:** Fluoroquinolone resistance with high-level moxifloxacin resistance
- **Case 3:** Combined resistance to rifampicin, isoniazid (katG mutation), and fluoroquinolones

These findings indicated Pre-XDR tuberculosis in two patients.

Radiological Findings

Chest radiography demonstrated **advanced structural lung disease**, including:

- Bilateral fibrocavitatory lesions
- Chronic post-tuberculosis lung changes
- Extensive parenchymal destruction

These findings are consistent with long-standing pulmonary TB and recurrent disease.

Treatment Initiation

Based on the resistance profile and NTEP guidelines:

- **Case 1:** was started on Bedaquiline, Levofloxacin, Linezolid, Cycloserine, and Clofazimine.
- **Case 2:** was treated with Bedaquiline, Linezolid, Delamanid, Cycloserine, and Clofazimine due to fluoroquinolone resistance.
- **Case 3:** was initiated on Bedaquiline, Linezolid, Delamanid, Cycloserine, and Clofazimine considering resistance to isoniazid, rifampicin, and fluoroquinolones.

Pyridoxine was added in all patients to prevent neurotoxicity.

Clinical Implications

The cases illustrate the complex interplay of previous TB infection, structural lung damage, addictions, and comorbidities leading to recurrent drug-resistant tuberculosis. Molecular diagnostics enabled rapid identification of resistance patterns, allowing timely initiation of individualized regimens under NTEP.

These cases highlight the importance of early detection of drug resistance, adherence to treatment protocols, and management of comorbid conditions to improve outcomes in DR-TB.

Table 1: Case Summary

Variable	Case 1	Case 2	Case 3
Age/Sex	34/M	48/M	65/M
Past TB	>5 years, recurrent	12 years back	Past TB (details unknown)
Addictions	–	Alcohol + Smoking	Alcohol + Ganja
Comorbidities	–	–	DM, HTN
GeneXpert	MTB+, Rif R	MTB+, Rif R	MTB+, Rif R
LPA	RR	FQ resistant + Mfx high resistance	INH + Rif + FQ resistant
Regimen	BDQ, Lfx, Lnz, Cs, Cfz	BDQ, Lnz, DLM, Cs, Cfz	BDQ, Lnz, DLM, Cs, Cfz
Program	NTEP	NTEP	NTEP

Treatment Strategy

All patients were started on individualized all-oral longer regimens under NTEP:

- Core drugs: Bedaquiline + Linezolid
- Companion drugs: Delamanid (where indicated), Cycloserine, Clofazimine
- Pyridoxine supplementation
- Management of comorbidities (DM, addictions)
- Monitoring: QTc, neuropathy, cytopenias [6,7]

Table 2: Individualized All-Oral Regimens and Key Monitoring

Case	Core Drugs	Companion Drugs	Key Monitoring & Safety
1	BDQ + LNZ	Lfx, Cs, Cfz + Pyridoxine	ECG (QTc), CBC (LNZ), neuropathy
2	BDQ + LNZ + DLM	Cs, Cfz + Pyridoxine	ECG (QTc with BDQ/DLM), CBC
3	BDQ + LNZ + DLM	Cs, Cfz + Pyridoxine	ECG, CBC, neuropathy, glycemic control

Abbreviations: BDQ – Bedaquiline; LNZ – Linezolid; DLM – Delamanid; Lfx – Levofloxacin; Cs – Cycloserine; Cfz – Clofazimine; DOE – Dyspnea on exertion.

Summary

This case series highlights three adult male patients with recurrent pulmonary tuberculosis complicated by rifampicin-resistant and fluoroquinolone-resistant disease, managed at a tertiary tuberculosis referral center in Mumbai under the National TB Elimination Programme (NTEP). All patients had a history of previous tuberculosis and presented with persistent respiratory symptoms including cough, fever, breathlessness on exertion, and generalized weakness.

Molecular diagnostic testing using Xpert MTB/RIF and Line Probe Assay (LPA) confirmed rifampicin resistance in all cases, with two patients demonstrating fluoroquinolone resistance suggestive of Pre-XDR tuberculosis. Radiological evaluation revealed fibrocavitatory lung disease and extensive structural damage, indicating long-standing pulmonary tuberculosis.

Individualized all-oral longer regimens containing newer anti-tuberculosis drugs such as Bedaquiline, Linezolid, Delamanid, Cycloserine, and Clofazimine were initiated in accordance with national guidelines. The clinical profiles of these patients illustrate the complex interaction of previous TB, addictions, comorbidities, and structural lung disease, all of which contribute to the development and recurrence of drug-resistant tuberculosis.

These cases emphasize the importance of rapid molecular diagnostics, individualized treatment strategies, and comprehensive management of associated risk factors in the control of recurrent DR-TB.

Conclusion

Recurrent pulmonary tuberculosis remains a major challenge in high-burden settings, particularly when complicated by drug resistance and extensive lung destruction. This case series demonstrates that patients with prior tuberculosis, addiction history, and comorbid conditions such as diabetes are at increased risk of developing rifampicin-resistant and fluoroquinolone-resistant tuberculosis.

Early identification of drug resistance through molecular diagnostic tools such as Xpert MTB/RIF and Line Probe Assay allows timely initiation of effective therapy. The availability of all-oral regimens containing newer drugs such as Bedaquiline and Delamanid has significantly improved treatment options for patients with DR-TB.

However, successful management requires more than pharmacological treatment. Comprehensive care including adherence support, management of comorbidities, nutritional support, addiction control, and infection prevention measures is essential.

Strengthening early diagnosis, improving treatment adherence, and addressing social determinants of health will be crucial steps toward achieving the goal of tuberculosis elimination.

Limitations of the Study

This case series has several limitations. First, the study includes a small number of patients, which limits the generalizability of the findings. Larger observational studies are required to better understand the patterns of recurrence and drug resistance in tuberculosis.

Second, the study design is retrospective, and some clinical details from previous tuberculosis episodes were not available in complete documentation. This limited the ability to analyze the exact causes of relapse or reinfection.

Third, long-term treatment outcomes and follow-up data were not fully available at the time of analysis, which restricts the ability to evaluate final treatment success or relapse rates.

Fourth, advanced molecular epidemiological techniques such as whole genome sequencing were not performed, which could have helped distinguish between relapse and reinfection.

Despite these limitations, the cases provide valuable insights into real-world clinical challenges in the management of recurrent drug-resistant tuberculosis in high-burden settings.

Preventive Measures

- Early molecular testing for all retreatment TB cases [14]
- Adherence support and counseling
- De-addiction interventions
- Nutritional and psychosocial support
- Household contact screening and TB preventive therapy [16]

Way Forward

- Strengthening early DR-TB detection at primary care level
- Integration of TB care with NCD and de-addiction services
- Community-based adherence support
- Programmatic surveillance of emerging resistance patterns
- Research into host genetic susceptibility and pharmacogenomics [17]

Take Home Messages

- Recurrent TB and addictions predispose to Pre-XDR TB.
- Xpert MTB/RIF and LPA must be done early in all retreatment cases.
- All-oral newer regimens under NTEP are life-saving when individualized.
- Comorbidity and addiction management is crucial for success.
- DR-TB is not only a medical problem but a social and public health emergency.

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