Original Article

Multidrug-resistant tuberculosis in Rawalpindi, Pakistan

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Abstract

Introduction: Multidrug-resistant (MDR) tuberculosis (TB) strains are resistant to isoniazid and rifampicin. Clinical characteristics, drug susceptibility patterns, and outcomes of MDR-TB patients treated at Holy Family Hospital, Rawalpindi, Pakistan, were studied from January 2007 to April 2010.

Methodology: Thirty diagnosed patients (60% male and 40% female) of MDR pulmonary TB were included. Each patient was treated according to WHO guidelines and followed for two years. Clinical characteristics (age, gender, literate or illiterate educational status, employment status, and income), drug susceptibility testing (DST) reports, and outcome (cured, treatment failure, default, and died) of each patient was noted.

Results: Mean patient age was 36.2 ± 15.4 years. In total, 60% patients were illiterate, 60% employed, 60% had income < Rs 5000 (42 Euro per month), 73.3% lived in an overcrowded residence, 60% were smokers, and 83.3% had taken anti-tuberculosis therapy previously. DST of MDR-TB strains for ethambutol, pyrazinamide, and streptomycin showed high resistance (> 60%). Except for ofloxacin and ciprofloxacin, < 20% resistance was noted in second-line anti-tuberculosis agents. Overall, 10% of patients were cured, 40% died, 20% had treatment failure, and 30% patients defaulted.

Conclusion: Pulmonary MDR-TB in Rawalpindi, Pakistan, is common in young males, poverty related circumstances, and has poor outcome. DST shows high resistance to first- line anti-tuberculosis agents and quinolones

Key words: multidrug resistant tuberculosis; disease attributes; drug sensitivity test; outcome assessment

Introduction

More than two billion people, equal to one-third of the world's population, are infected with *Mycobacterium tuberculosis* bacilli. One in 10 people with tuberculosis (TB) develop active TB. Each year about 1.8 million people die due to TB, which equals 4,500 deaths per day, most of which occur in heavily populated Countries, such as Pakistan, China, India, Bangladesh, and Indonesia where the majority (48%) of new cases of TB occur [1]. In Pakistan approximately 297,000 TB cases are diagnosed per year.

Multidrug resistant (MDR) TB is a form of TB characterized by to the two most potent first-line antituberculous medicines, isoniazid and rifampicin. On a worldwide basis, there are an estimated 440,000 cases of MDR-TB per year; this is equivalent to 3.6% of all new TB patients. According to the World Health Organization (WHO), Pakistan is one of 27 countries with a high burden of MDR-TB. Approximately 2% to 3.2% of newly diagnosed and 35% of previously treated Pakistani patients have MDR-TB [2]. Cure rates in MDR-TB are low compared to drug-susceptible TB [3,4].

In Pakistan, MDR-TB patients are frequently managed at the Medical Unit of Rawalpindi Medical College, Rawalpindi. This study presents our recent experience with MDR-TB patient management in terms of clinical characteristics, drug susceptibility patterns, and outcomes.

Methodology

This cross-sectional, observational study was conducted with the permission of the Departmental Ethical Committee at the Medical Unit of Rawalpindi Medical College, Rawalindi, from January 2007 to April 2010. Pulmonary TB patients were screened for MDR-TB if 1) they had extensive, bilateral, cavitating disease; 2) they were not improving clinically, radiologically, and microbiologically (not becoming smear negative),

Table 1. Results of drug susceptibility testing of multidrug-resistant tuberculosis strains

Medication	Susceptible (n, %)	Resistant (n, %)
First-line drugs		
Ethambutol	8 (33.4)	22 (66.6)
Pyrazinamide	6 (20)	24 (80)
Streptomycin	6 (20)	24 (80)
Second-line drugs		
Amikacin	26 (86.7)	4 (13.3)
Ofloxacin/ciprofloxacin	16 (53.3)	14 (46.7)
Ethionamide	26 (86.7)	4 (13.3)
Capreomycin	30 (100)	0
Kanamycin	26 (86.7)	4 (13.3)

specifically in settings of retreatment and previous default of antituberculous therapy (ATT); and 3) they were contacts of MDR-TB patients. Screening was performed by testing cultures obtained from sputum and/or endobronchial washings (where relevant) for drug susceptibility testing (DST). MDR-TB was diagnosed when *M. tuberculosis* isolates were resistant to both isoniazid and rifampicin.

MDR-TB patients all provided informed consent. Patient management consisted of 1) modified ATT guided by DST for about two years according to WHO guidelines; 2) treatment of other/associated pulmonary diseases such as chronic bronchitis, asthma, bronchiectasis, fibrosis, pneumothorax, and respiratory failure; 3) treatment/control of associated diseases such as diabetes mellitus, hypertension, and ischemic heart disease, *etc.*; 4) general care including nutritional support, physiotherapy, and deep venous thrombosis prophylaxis wherever relevant; 5) side-effect/medication tolerance monitoring; and 6) provision of disease-related information and counseling. Patients were managed on both in- and outpatient basis depending on their clinical scenario.

Complete blood counts, renal function tests, and liver function tests were performed at induction and each following month until the end of the study. Chest X rays were performed at 6-month intervals and in cases of concurrent illnesses. Sputum smear and cultures were taken monthly [4].

The following WHO criteria were used for outcome evaluation: 1) Cured: a patient who completed a course of ATT and was culture-negative in the last month of treatment and had been culture-negative during the preceding 11 months of treatment; 2) Treatment Completed: a patient who completed treatment but did not meet the definition for *cure* or *failure* due to lack of bacteriologic results; 3) Treatment Failure: a patient who had more than one positive culture in the last 12 months of treatment, with a minimum of five cultures performed during the last 12 months, or a patient who remained persistently culture-positive and a clinical decision was made to terminate treatment early; 4) Death: a patient who died of any reason during treatment; and 5) Treatment Default: a patient whose treatment was interrupted for two or more consecutive months due to any reason, including patients who left against medical advice [4].

Data regarding patient age; gender; place of residence; overcrowding (when two or more people were sleeping in the same room, except when they were married or were less than ten years old); educational status; occupation; monthly income smoking; presence or absence of other diseases/conditions; previous ATT and adherence to therapy; DST; and outcome were analyzed descriptively using the Statistical Package for the Social Sciences (SPSS) version 15 (IBM SPSS, Armonk, NY, USA). Mean ± standard deviation was calculated for age. Frequency and percentage were calculated for categorical variables such as gender, place of residence, DST, and outcome.

Results

Of 45 patients who were screened for MDR-TB, 30 (66.6%) diagnoses were confirmed based on DST and were included in the study. Screenings for human immunodeficiency virus infection were negative in all 30 patients. Eighteen (60%) of these were male and 12 (40%) female. Mean patient age was 36.2 ± 15.4 years. Nine (30%) patients were residents of the inner city area of Rawalpindi, while 21 (70%) belonged to adjoining towns and villages.

Table 2. Outcome comparison of multidrug-resistant tuberculosis cases in various regional studies

Country	No. of Patients	Cured (%)	Treatment failure (%)	Default (%)	Died (%)	LAMA* (%)
Pakistan[3]	579	39.2	0.51	41.2	4.83	14.33
Pakistan[8]	176	90.22				
Pakistan[9]	70	55	10		2	21
India[5]	52	69.2	7.7	11.5	11.5	
Iran[10]	17	63.7**	23.5		5.9	
Bangladesh[11]	58	69	5	12	14	
Russia[12]	244	77	7	12	5	
Our Study	45	10	20	30	40	

*LAMA - Left against medical advice; **Includes 23.5% probable cure patients

Twenty-two (73.3%) patients lived in overcrowded residences. Eighteen (60%) patients were illiterate; 18 (60%) were employed; and 18 (60%) patients had a monthly income of less than Rs 5000 (42 Euro) per month. Eighteen (60%) patients were smokers and 25 (83.3%) patients suffered from one or more pulmonary diseases or complications, such as chronic bronchitis, asthma, bronchiectasis, fibrosis, pneumothorax, and respiratory failure. Seven (23.4%) patients had non-pulmonary diseases, such as diabetes mellitus, and hypertension. Twenty-nine (96.6%) patients had previously taken ATT and 19 (65.5%) of these took ATT irregularly or incompletely.

Drug susceptibility testing of first-line antibiotics including ethambutol, pyrazinamide, and streptomycin showed high co-resistance patterns (> 50% of patients). Except for ofloxacin and ciprofloxacin, less than 20% resistance was noted for second-line antibiotics. DST results are detailed in Table 1. Thirteen (43.3%) patients developed adverse effects from therapy and were managed accordingly. Patient outcomes were as follows: , 3 (10%) patients were cured, 6 (20%) patients had treatment failure, 9 (30%) patients defaulted, and 12 (40%) patients died. Sepsis, respiratory failure, and pulmonary embolism were probable causes of death in patients who expired.

Discussion

The cure rate for MDR-TB is considered to be 70–90% [5]. Mortality in patients with MDR-TB can be up to 60% [6]. Cure rates and mortality are, however, lower in HIV-infected persons [7]. In our study of MDR-TB patients, 10% were cured, 40% died, 20% had treatment failure, and 30% defaulted. A comparison of our results with those of other studies conducted locally and in regional countries is given in Table 2. The high mortality and low cure rates in our study can be attributed to three main factors that affected our patients; 1) extensive lung damage; 2) high resistance to remaining first-line ATT medications; and 3) additional pulmonary complications, including chronic bronchitis, asthma, bronchiectasis, fibrosis, pneumothorax, and respiratory failure. Most of our patients (83.3%) suffered from at least one of these conditions.

MDR-TB isolates were resistant to ethambutol in 66% of our patients, to pyrazinamide in 80%, and to streptomycin in 80%. We noted high resistance to ofloxacin and ciprofloxacin, which was probably due to the excessive and rash use of these antibiotics in our scenario. Three Pakistani studies similar to ours have been previously published. In one of these, resistance to pyrazinamide and ethambutol was 10.79% and 17.61%, respectively in MDR-TB patients, but DST of second-line antibiotics was not available [8]. In the second study, MDR-TB isolates were resistant to 6 first-line ATT medications in 38% of the cases, to 5 medications in 20% of the cases, to 4 medications in 25% of the cases, and to 3 medications in 12% of the cases. DST of second-line antibiotics was also not available in this study [9].

Treatment default in TB ranges from 6-30%.[13] Treatment default in our patients was 30%. Intolerance to second-line ATT, lack of early improvement in clinical features, and the high cost of therapy/tests were common reasons for default in our patients. Of these, cost of therapy/tests was most distressing as the other two are expected in MDR-TB scenario. No DST facility was available in our tertiary care public hospital, and DST of second-line ATT was available only at the Agha Khan Laboratory. Second-line medications in most

instances were provided through Zakat (obligatory payment made once a year under Islamic law which is used for charity and religious purposes) and/or Bait-ul-Mal (a government run department to help the poor), and philanthropists.

Treatment failure in MDR-TB's context has grave consequences. Disease progress results in complications causing death. End-of-life supportive measures are required for these patients. Additionally, they are potential sources of disease spread. Most patients who defaulted will ultimately be included in the treatment failure group, which increases our treatment failure group to an alarmingly high figure (~50%).

Most of our patients were males in their thirties. Overcrowded living conditions, illiteracy, poor socioeconomic status, and smoking were noted in more than 50% of our patients. Furthermore, 96.6% of our patients were treated for TB previously, and 65.5% of these took ATT irregularly or incompletely. These characteristic of TB and MDR-TB patients have been noted earlier as well [14].

The cost of treating an MDR-TB patient in the developed world is around £60,000 (approximately US $100,000 or 900,000 Pakistani Rs) [15]; therefore, managing such patients at public sector hospitals is extremely difficult in resource-limited settings. Measures that focus on the efficient treatment of non drug resistant TB must be taken to help control and to prevent the development and spread of MDR-TB.

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