

THE EMERGENCE OF FLUOROQUINOLONES RESISTANCE AMONG MDR-TB PATIENTS AT A TERTIARY CARE FACILITY IN SIALKOT

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Abstract: Pakistan is one of the countries that has a very high rate of multidrug-resistant tuberculosis (MDR-TB). The rising rate of drug resistance can be linked to several issues, including the private sector that is inadequately regulated, an increase in the number of prescribed antibiotics, and the practice of self-medication. A national anti-tuberculosis medication resistance survey found a high prevalence of fluoroquinolone resistance in multidrug-resistant tuberculosis patients. The purpose of this study was to evaluate fluoroquinolone resistance among multi drugs resistant TB patients. This study looked at the records of drug susceptibility testing, known as DST, for a total of 276 patients at Govt. Allama Iqbal memorial teaching hospital Sialkot, who was receiving treatment for tuberculosis. Eight-six patients fulfilling the inclusion criteria were included in the final analysis. The incidence of fluoroquinolone (ofloxacin) resistance was investigated, and its association with demographic factors and previous TB treatment categories was studied. When assessing fluoroquinolone resistance on DST, 44 (51.2%) patients resisted levofloxacin and 11 (12.8%) with moxifloxacin. In our study, the fluoroquinolones resistance was not statistically different in Cat-1 and Cat-2 patients. Similarly, age and gender also showed no significant difference in resistance to moxifloxacin and levofloxacin in MDR-TB patients. An alarmingly high percentage of MDR-TB infections showed resistance to fluoroquinolones. Based on our findings, it may be necessary to reevaluate current treatment recommendations for multidrug-resistant tuberculosis. There is an immediate need for stricter pharmacy regulations and better responsible involvement of private healthcare providers.

Keywords: Fluoroquinolones, Tuberculosis, Multidrug-Resistant, Drug Resistance, Microbial, Antibiotic Resistance, Mycobacterium tuberculosis

Introduction

Tuberculosis (TB) is one of the most common infectious diseases, and it causes serious illness and death. A high percentage of the global population is infected with tuberculosis, with the vast majority of infections occurring in underdeveloped countries. New forms of medication resistance constitute a significant problem for tuberculosis (TB) treatment worldwide (Zegeye et al., 2019). According to the World Health Organization (WHO), MDR-TB cases increased to 450,000 worldwide in 2012 (Organization, 2013). Pakistan ranks fifth among the top 30 nations with a high TB burden, according to the WHO Report 2020. From 2019 projections by WHO's Eastern Mediterranean Regional Office (EMRO), we may infer that there are roughly 265 TB infections in Pakistan for every 100,000 persons. Furthermore, during the first nine months of 2020, Pakistan had 15,5537 TB cases (new and relapsed) (Cooke et al., 2019). The spread of multidrug-

resistant (MDR) strains of tuberculosis (TB), even though the disease has an 85% cure rate and may be prevented, is a significant problem. Regarding the prevalence of multidrug-resistant tuberculosis, Pakistan is ranked fourth out of the 27 nations studied (Dheda et al., 2017). The average price tag associated with treating tuberculosis in Pakistan is \$307.74. In recent years, there has been an increase in the prevalence of drug-resistant tuberculosis (also known as XDR-TB) across the nation (Laurence et al., 2015). This particular strain of the disease is resistant to a number of different medications, including fluoroquinolones and at least one other second-line injectable (Hasan et al., 2010). Because fluoroquinolones are so commonly used to treat upper respiratory tract infections, the widespread development of resistance to this class of antibiotics is a significant cause of concern for the public's health. Fluoroquinolone overprescribing by general

practitioners, over-the-counter sales of fluoroquinolones at private pharmacies, and patient self-medication are all common occurrences (Jabeen et al., 2011). In Pakistan, the private healthcare industry is prevalent but only loosely supervised. The first Pakistani national investigation on drug-resistant tuberculosis found that 26.6 percent (95 percent CI 18.0-36.7) of a sample of 96 MDR-TB patients were resistant to fluoroquinolones (Tahseen et al., 2016). According to the researchers' findings, the percentage of MDR-TB patients who exhibited resistance to fluoroquinolones increased from 17.4 percent in 2005 to 53.9 percent in 2014 (Ahmad et al., 2015). The growing fluoroquinolone resistance poses a serious challenge to the effective treatment of multidrug-resistant tuberculosis (MDR-TB) patients, which indicates that it is essential for Pakistan to expand its Program for the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) (Ullah et al., 2020). Patients require empirical medication since the findings of standard drug-susceptibility testing (DST) for fluoroquinolones and other second-line medicines can take anywhere from six weeks to eight weeks to become available. Patients and healthcare providers may become concerned if they do not see a positive clinical response to treatment (Rich and Jaramillo, 2008). As a result of the increased prevalence of fluoroquinolone resistance, it is required for the MDR-TB program to conduct a review of the combinations of empirical therapy that are currently being used. More institutional evidence of fluoroquinolone medication resistance among MDR-TB patients will benefit national efforts to avoid antibiotic resistance. These initiatives are already making progress. This research aimed to identify the emergence of fluoroquinolone resistance among MDR-TB from a tertiary care hospital in Sialkot.

Methodology

This retrospective study was conducted at Govt. Allama Iqbal memorial teaching hospital Sialkot from 2020 to 2022. A total of 276 patients were selected for the analysis who were treated with anti-tuberculosis treatment. The demographic parameters, including age and gender, were taken from the medical record of the patients. All Mycobacterium tuberculosis (MTB) isolates obtained from pulmonary and extra-pulmonary samples received between 2019 and 2021 were analyzed through drug susceptibility testing (DST). DST results showed 86 patients had multi-drug resistance. So, the 86 confirmed cases of MDR-TB on DST were included for further analysis. Patients with mono-drug resistance or who did not fit the MDR-TB definition were excluded from the study. We also collected the data of DST for second-line anti-tuberculous drugs

such as fluoroquinolones. Based on the treatment regimen each patient received, they were further classified into the category I (a treatment regimen consisting of four different anti-TB drugs) or category II (a treatment regimen consisting of four other anti-TB drugs and streptomycin). The ethical review board of the institute gave their authorization to proceed with this project. SPSS 25.0 was utilized to do data analysis. For age and gender, descriptive statistics were used. The mean and standard deviation were used to compute the quantitative variables. The association of levofloxacin and moxifloxacin (fluoroquinolone) resistance with age was investigated using Student's t-test. Chi-squared tests were conducted to examine the association of levofloxacin and moxifloxacin resistance with gender. A P-value of 0.05 or lower was considered statistically significant by the researchers.

Results

A total of 86 confirmed cases of multi-drug resistance TB on DST were included in this study. The mean age of the group was 37.8± 17.2. In our research, 59.3% were males. The age group-wise distribution is shown in table 1. 43% of patients were aged 15- 30.

Table 1 Demographic variables:

Variables	Construct	Frequency (n)	Percentage (%)
Gender	Male	51	59.3
	Female	35	40.7
Age (years)	< 15 Years	2	2.3
	15-30 Years	37	43.0
	31-45 Years	14	16.3
	> 45 Years	33	38.4

When assessed fluoroquinolones resistance on DST, 44 (51.2%) patients had resistance to levofloxacin and 11 (12.8%) with moxifloxacin (Figure 1)

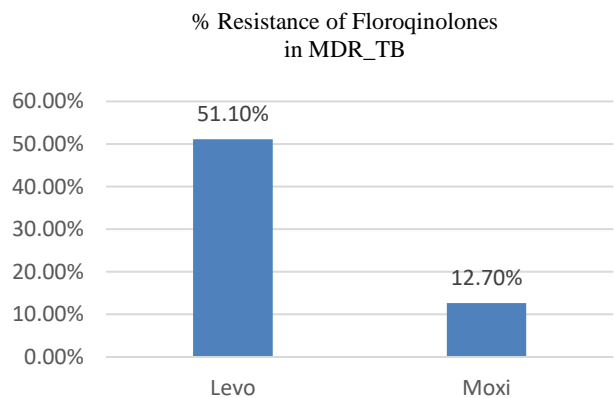


Figure 1: Resistance of Fluoroquinolones in MDR_TB

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Among first-line drugs, in 40.1% of patients, pyrazinamide was found resistant, followed by streptomycin (36%) and ethambutol (16.3%). Table 2

Table-2 Resistance First-line anti-tuberculous medication among MDR-TB patients

First-line Drugs	Frequency (n)	Percentage (%)
HR-Z	35	40.1
HR-S	31	36.0
HR-E	14	16.3

In our study, the fluoroquinolones resistance was not statistically different in Cat-1 and Cat-2 patients. Similarly, age and gender also showed no significant difference in resistance to moxifloxacin and levofloxacin in MDR-TB patients.

Discussion

Fluoroquinolone resistance is on the rise in Pakistan, as shown by our study and others, including the national anti-TB medicine resistance study (Ahmad et al., 2016). This analysis, carried out at a facility specializing in treating MDR-TB patients, supports the hypothesis that MDR-TB patients exhibit a high prevalence of fluoroquinolone resistance. It was shown that resistance was not related to demographic factors such as age, gender, or previous TB treatment history; this finding suggests that it may be highly prevalent amongst this population.

To improve treatment outcomes and prevent the development of new drug resistance, it may be essential to reevaluate the current recommendations for treating MDR-TB. Numerous public health policy approaches and programmatic initiatives are helpful in this setting. To begin, there must be strict controls on the use of antibiotics, particularly fluoroquinolones. Considering the size and disarray of Pakistan's private healthcare industry, this will likely be a significant obstacle. Although it may be challenging to put into practice, regulation is needed to limit the selling of antibiotics over the counter. Second, more in-depth approaches to include the private sector suppliers must be investigated. The National TB Control program's recent proposals appear promising and look seriously into the matter (Chughtai et al., 2013). Local networks and partnerships can be established under unique public-private mix models, allowing private physicians to get medication for patients through provincial TB control programs in exchange for increased case notification. More should be done to coordinate with primary care doctors, particularly urban family doctors who work in smaller practices (Shelby et al., 2017). The National Tuberculosis Program (NTP)

suggests that training be held on the diagnosis and treatment of TB cases and the more prudent use of antibiotics for the treatment of common diseases, with a particular emphasis on limiting the overuse of fluoroquinolones. These training courses should be held at least once every two years (Organization, 2022). It is important that professional organizations representing medical specialists such as pulmonologists, infectious disease specialists, and pharmacists, amongst others, do a better job of disseminating this knowledge to both medical professionals and the general public (Vanaja et al., 2016). Lastly, the MDR-TB program will need to take further measures to strengthen case-holding and guarantee all enrolled patients' complete treatment as the number of PMDT services across the country continues to rise. Food baskets and other incentives for treatment compliance are only two examples of community-based solutions and behavioral economics strategies that may be useful (Khan et al., 2012). Increasing the number of people who have access to MTB/RIF testing at the point of care will help prevent the spread of resistant strains and enhance treatment outcomes. This can be accomplished without compromising patient care. Due to a lack of DST data for fluoroquinolones of the third and fourth generations, it was not possible for this experiment to identify whether or not *M. tuberculosis* iso-lates are cross-resistant to ofloxacin. Due to a lack of available patient history, such as past quinolone usage, further research into the risk factors and clinical correlates of fluoroquinolone resistance was limited. This included both the risk factors and clinical correlates of fluoroquinolone resistance. In order to determine the connection between fluoroquinolone resistance and the outcomes of treatment for multidrug-resistant tuberculosis, additional studies are required.

Conclusion

An alarmingly high percentage of MDR-TB infections showed resistance to fluoroquinolones. Based on our findings, it may be necessary to reevaluate current treatment recommendations for multidrug-resistant tuberculosis. There is an immediate need for stricter pharmacy regulations and better responsible involvement of private healthcare providers.

Conflict of interest

The authors declared no conflict of interest.

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