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Resistance patterns, prevalence, and predictors of fluoroquinolones resistance in multidrug resistant tuberculosis patients

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ABSTRACT

Background: Fluoroquinolones are the backbone of multidrug resistant tuberculosis treatment regimens. Despite the high burden of multidrug resistant tuberculosis in the country, little is known about drug resistance patterns, prevalence, and predictors of fluoroquinolones resistance among multidrug resistant tuberculosis patients from Pakistan.
Objective: To evaluate drug resistance patterns, prevalence, and predictors of fluoroquinolones resistance in multidrug resistant tuberculosis patients.
Methods: This was a cross-sectional study conducted at a programmatic management unit of drug resistant tuberculosis, Lady Reading Hospital Peshawar, Pakistan. Two hundred and forty-three newly diagnosed multidrug resistant tuberculosis patients consecutively enrolled for treatment at study site from January 1, 2012 to July 28, 2013 were included in the study. A standardized data collection form was used to collect patients' socio-demographic, microbiological, and clinical data. SPSS 16 was used for data analysis.
Results: High degree of drug resistance (median 5 drugs, range 2–8) was observed. High proportion of patients was resistant to all five first-line anti-tuberculosis drugs (62.6%), and more than half were resistant to second line drugs (55.1%). The majority of the patients were ofloxacin resistant (52.7%). Upon multivariate analysis previous tuberculosis treatment at private (OR = 1.953, $p = 0.034$) and public private mix (OR = 2.824, $p = 0.046$) sectors were predictors of ofloxacin resistance.
Conclusion: The high degree of drug resistance observed, particularly to fluoroquinolones, is alarming. We recommend the adoption of more restrictive policies to control non-prescription sale of fluoroquinolones, its rational use by physicians, and training doctors in both private and public–private mix sectors to prevent further increase in fluoroquinolones resistant *Mycobacterium tuberculosis* strains.

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Introduction

Multidrug resistant tuberculosis (MDR-TB) defined as resistance to both isoniazid (H, INH) and rifampicin (R, Rif) is a major barrier to achieve successful TB control. Both INH and Rif are the most effective anti-TB drugs and the backbone of first line anti-TB treatment. Resistance to INH and Rif leads treatment with less potent, more toxic and expensive second-line anti-TB drugs (SLD). Fluoroquinolones (FQ) — broad spectrum antibiotics — have been shown to be useful in TB treatment — have been used in TB care since 1984, and have become integral part of drug resistant TB treatment regimens.[1] Various studies have reported positive associations between FQ resistance and poor treatment outcomes in MDR-TB.[2–5] Unfortunately, Pakistan in addition to be the 5th highest country of TB burden also harbors the largest population of MDR-TB patients in Eastern Mediterranean Region of WHO. It is estimated that 9900 (95% confidence interval [CI]: 6400–13,300) new MDR-TB cases emerged in Pakistan in 2013 with an estimated proportion of 4.3% (95% CI: 2.8–5.7) of new cases and 19% (95% CI: 14–25) of previously treated TB cases.[6] This situation is further worsened by reportedly increased FQ resistance in drug resistant TB in the country.[7,8] Few studies from Pakistan have evaluated the prevalence of FQ resistance in MDR-TB patients,[7–10] but to the best of our knowledge none has evaluated predictors of FQ resistance in MDR-TB patients. Therefore, the present study was conducted with the aim to evaluate patterns of drug resistance, prevalence, and predictors of FQ resistance among MDR-TB patients.

Materials and methods

Study design and settings

This was a cross-sectional study conducted at a programmatic management unit of drug resistant TB (PMDT), Lady Reading Hospital (LRH) Peshawar, Pakistan. At the time of study initiation, PMDT unit LRH was the only center in Khyber Pukhtoonkhwa (one of the four provinces of Pakistan) where drug resistant TB was treated. All MDR-TB patients consecutively enrolled for treatment at the study site from January 1, 2012 to July 28, 2013 were included in the study. Since October 1, 2012 data were collected prospectively while before October 1, 2012 data were collected retrospectively. Patients with mono, poly, and extensive drug resistant TB (XDR-TB) and/or history of previous treatment of drug resistant TB were excluded.

Drug resistant TB (DR-TB) suspects referred to the study site were initially evaluated with two sputum samples for acid fast bacilli (AFB) by direct sputum smear microscopy using Ziehl Neelsen staining method and GeneXpert System's MTB/Rif (*Mycobacterium tuberculosis*/rifampicin). Upon positive smear microscopy and GeneXpert System's MTB/Rif, sputum samples were sent to Aga Khan University Hospital Laboratory for sputum culture and DST. Susceptibility testing for isoniazid (H), rifampicin (R), ethambutol (E), streptomycin (S), ofloxacin (Ofx), amikacin (Am), kanamycin (Km), ethionamide (Eto), and capreomycin (Cm) was conducted by using agar proportion method on enriched Middle brook 7H10 medium (BBL, Beckton Dickinson). Pyrazinamide (PZA, Z) susceptibility test was carried out by using BACTEC Mycobacterial Growth Indicator Tube (Becton Dickinson Diagnostics, Sparks, MD, USA) in accordance with manufacturer's instructions. A standardized data collection form was used to collect patients' socio-demographic, microbiological, and clinical data.

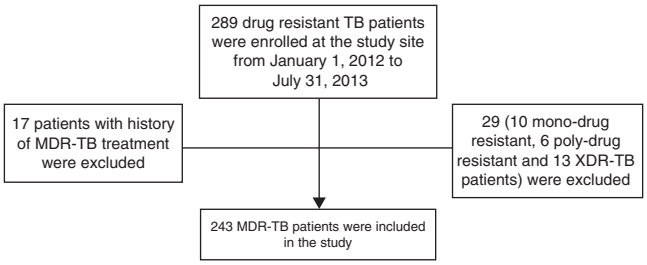

Fig. 1 – Inclusion and exclusion of study patients. MDR-TB, multidrug resistant tuberculosis; XDR-TB, extensive drug resistant tuberculosis.

Statistical analysis

Statistical Package for Social Sciences (SPSS 16) was used for data analysis. Means and standard deviations were calculated for continuous variables, whereas categorical variable were presented as frequencies and percentages. Chi-squared test was used to observe association between categorical variables. Multivariate logistic regression analysis with Wald statistical criteria using the backward elimination method was used to obtain a final model describing the predictors FQ resistance. A p-value of <0.05 was considered statistically significant. Relevant variables with p-value <0.2 in univariate analysis were included in multivariate analysis. We checked correlation among variables entered in multivariate analysis.

Ethical approval

The study was approved by the Research and Ethics Committee of Postgraduate Medical Institute, Peshawar, Pakistan. Prior to beginning of the study, written consent was taken from patients who were able to do so. In case of illiteracy the purpose of study was explained to the patients in their native language, and next a kin or treatment supporter gave written consent on behalf of the patient. This consent procedure was approved by Research and Ethics Committee.

Results

During the study period a total of 289 drug resistant TB patients were enrolled at the study site. A total of 46 patients were excluded: 29 with drug resistant TB other than MDR-TB (10 with mono-drug resistant TB, six with poly-drug resistant, and 13 with extensive drug resistant) and 17 with history of previous treatment for MDR-TB (Fig. 1).