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Original Article

Multidrug-resistant tuberculosis: Need for better diagnostic modalities and clinical end points – Five-year tertiary care hospital experience

Jolsana Augustine [a,*], *Neeraj Jain* [b], *Chand Wattal* [c], *Reena Raveendran* [c], *Bobby Bhalotra* [b]

[a] *Kerala Institute of Medical Sciences, India*
[b] *Department of Chest Medicine, Sir Ganga Ram Hospital, New Delhi, India*
[c] *Department of Microbiology, Sir Ganga Ram Hospital, New Delhi, India*

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ABSTRACT

Aims: Multidrug-resistant tuberculosis (MDR-TB), a manmade disaster, is a threat to effective control of TB in resource-limited countries like India. The main aim was to study the resistance pattern of MDR-TB patients and their treatment outcome along with the drug-related adverse effects.

Methods: Patients who have completed treatment or expected to complete within the study period (2007–2012) diagnosed after January 2007 and on regular follow-up were screened. A total of 40 MDR-TB patients (28 pulmonary and 12 extra-pulmonary) were enrolled. All sputum specimens or other extra-pulmonary specimens were cultured using automated liquid culture system. Microbiological confirmation of tubercular bacteria was done using molecular identification system. Drug sensitivity testing of these patients was done using both genotypic and phenotypic methods.

Results: 63% were resistant to INH and rifampicin, 20% HRS and 17% to HRSE. 55% patients already received anti-tuberculosis treatment and failed treatment at enrolment. The primary outcomes were favourable in 97% (cure and treatment completion). No statistical significance was observed on comparing treatment outcome with drug resistance pattern, category of TB and type of TB. Major drug-related adverse effects seen were hypothyroidism and mild gastrointestinal symptoms. A total of 9 patients (22%) with MDR mediastinal lymphadenopathy could be identified with endobronchial ultrasound (EBUS)-guided fine needle aspiration (FNA) and treated with good outcome.

Conclusion: Most of the patients if properly treated and surgically intervened at the right time can have successful recovery. Use of new modality like EBUS-guided FNA in diagnosing extra-pulmonary MDR-TB appears promising.

* *Corresponding author*. Tel.: +91 9446728953.
E-mail address: j_augustine08@ymail.com (J. Augustine).

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1. Introduction

Emergence of multidrug-resistant and extensively drug-resistant TB (MDR/XDR-TB) is a threat to effective control of tuberculosis. It is mostly a man-made problem due to inappropriate regimens, improper adherence and poor-quality drugs. An important aspect in MDR-TB treatment is the extensive monitoring required. It includes repeated cultures and smear analyses for judging adequate treatment response. World health organisation and Programmatic Management of Drug resistant Tuberculosis (PMDT) advocate frequent culture and sensitivity. This is based on the consideration that relying exclusively on smear examination may delay the diagnosis of multidrug resistance.[1] The quality of evidence suggesting this is low as most of them are from observational studies and modelling. In resource-limited countries like India, repeated cultures are not technically feasible due to high financial implications. The exact cost effectiveness and burden involved in frequent cultures are not known.[2] Although there are several studies looking into the prevalence and resistance pattern of MDR-TB patients,[3,4] their treatment outcome as defined by clinical cure and successful treatment completion is largely unreported. Some studies have proposed smear negativity as a surrogate marker of culture conversion, but the clinical end points of treatment are largely un-addressed. This study looks into the treatment outcome in TB, mostly on clinical grounds and smear monitoring. Our study also gives newer insights into how effective and early diagnosis of MDR-TB can be made using newer modalities like endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA).

2. Materials and methods

The study was conducted by a chart review in the department of respiratory medicine of a tertiary care hospital in New Delhi over a period of 5 years from January 2008 to December 2012. All patients in the study period diagnosed to be sputum positive or sputum negative extra-pulmonary MDR-TB were identified from hospital records. Patients included were culture proven multidrug-resistant pulmonary and extra-pulmonary TB. All cases of MDR-TB patients in whom anti-tuberculosis treatment (ATT) can be less effective due to other co-morbidities were excluded; known cases of congenital or acquired immunodeficiency, patients on anti-epileptic medications, patients with a body mass index (BMI) <15 kg/m^2 and those with decompensated liver disease were excluded. As the investigator did not come across patients, his or her consent was not taken. The study was approved by ethics committee of the institution.

2.1. Definitions

Standard WHO definitions for MDR-TB, XDR-TB, new case, relapse, default and failure were used.[5] Outcome definitions of cure, treatment completed, default and failure and death were used from recent PMDT guidelines.[6]

2.2. Patient selection

During the study period, a total of 49 MDR-TB cases were reviewed for enrolment out of which nine patients were excluded. Three of them had decompensated liver disease, five had diabetes mellitus and one had immunodeficiency. Data of 40 patients who fulfilled the inclusion criteria were analysed (Table 1). Detailed baseline clinical profiles including age, sex and BMI were recorded. Patients were clinically categorised as New, Relapse, Previous treatment failure, Default as well as according to the site of tubercular infection. The drug sensitivity pattern and duration of treatment were also recorded. In patients with pulmonary tuberculosis, isolation of Acid Fast Bacilli was attempted from sputum. In sputum negative patients, bronchoscopic lavage was taken and sent for culture. Real-time linear EBUS-guided TBNA was used to sample mediastinal lymph nodes. EBUS-guided fine needle aspiration was taken from possible accessible nodes and aspirate was sent for smear examination and culture. In patients with peripheral nodes, aspiration and excision biopsies were performed wherever feasible and sent for microbiological and histopathological examination. In patients with serosal involvement (pleural/ascitic/cerebrospinal) fluid was sent for biochemical and microbiological examination. All specimens were subjected to direct fluorescent staining and subsequently cultured using automated liquid culture system (BacT/ALERT 3D, bioMerieux, Durham, North Carolina, USA) as well as on Lowenstein Jensen slants after decontamination and concentration using N-acetyl-L-cystine NaOH method. Microbiological confirmation of tubercular bacteria was done using molecular identification system Accuprobe (Gen Probe, San Diego, California). Drug sensitivity testing of these patients was done using both genotypic and phenotypic methods. MTB-DR plus assay (Hain Life science GmbH, Nehren, Germany) was used for genotypic assay and rapid detection of rifampicin and INH resistance. This test was directly done in case of pulmonary specimens after digestion and decontamination. Extra-pulmonary specimens were subjected to culture and then MTB-DR plus assay was performed from culture isolates. All culture-positive isolates were subsequently subjected to phenotypic susceptibility testing using BacT/ALERT 3D system (1% proportion method) according to manufacturer's instructions. The critical concentrations used were 0.1 μg/ml for INH, 1 μg/ml for rifampicin, 1 μg/ml for streptomycin and 5 μg/ml for ethambutol.[7]

2.3. Treatment regimen and follow-up

Our standard regimen was based on 6 months of intensive phase of kanamycin, levofloxacin, ethionamide/prothionamide, cycloserine, ethambutol and pyrazinamide followed by continuation phase of 18 months omitting injectable drug and pyrazinamide. Ethambutol was also given in patients who showed resistance to the drug. The regimens were adjusted according to weight.[5] The regimen was used uniformly in all patients.

These patients were followed up monthly in the intensive phase and thereafter three monthly during the course of treatment and all clinical assessments and investigation reports regarding renal function, thyroid function were entered on the same proforma. Patients who defaulted on