Prevalence of Multi-Drug Resistant Tuberculosis among New Culture-Positive Pulmonary Tuberculosis Patients in Tertiary Care Center of North India

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Abstract

Introduction: As India aims to end Tuberculosis (TB) by 2025, increased prevalence of Multi-Drug Resistant (MDR) strains continues to be a major public health concern.

Methods: New case of Pulmonary TB (PTB) was defined as no history of Anti-Tuberculosis Therapy (ATT) intake in the past or taken ATT for <1 month. Single sputum specimen from 1103 suspected PTB cases was collected at two tertiary care referral centers in North India. All samples were subjected to Ziehl-Neelsen stain, culture using automated BACTEC MGIT™ 960™ and Drug Susceptibility Testing using Line Probe Assay. Resistance testing for Rifampicin and Isoniazid was done in all culture-positive patients.

Results: Of the total 1103 patients (Median Age 34 years, 59% and 41% males and females respectively), there were 683 new PTB cases with liquid culture positive. From these patients, 62 (9.1%) were resistant to rifampicin, 75 were resistant to isoniazid (11%) and 60 (8.7%) patients were resistant to both drugs.

Conclusion: There is a high burden of MDR strains among new PTB cases. A higher prevalence could be because centers were referral institutes.

Keywords: MDR-TB; Pulmonary tuberculosis; Drug susceptibility

Introduction

Tuberculosis (TB) remains a major global health problem. In 2016, World health organization (WHO) estimated 10.4 million people developed TB and 1.3 million died from the disease.1 Mortality of the disease was predominantly observed in Human Immunodeficiency Virus (HIV) co-infection, 3.6 million patients died due to HIV-TB co-infection. In 2016, there were 0.6 million new Rifampicin-Resistant TB (RRTB) cases, of which around 0.5 million had Multi-Drug Resistant TB (MDR-TB). Almost half (47%) of these cases were in India, China and the Russian Federation [1].

MDR-TB patients, especially with pulmonary infection pose a great challenge to public health since they have the potential to spread the strain to many close contacts. In addition, treatment of these patients requires long-term injectable drugs and can extend up to 27 months. Complete treatment, though effective, has a myriad of life-threatening side effects and is dependent on a large part to the psycho-social environment of the patient. Detection and early-treatment of these patients become imperative if the goal of ending TB epidemic is to be realized anytime in the near future.

The primary objective of this study, therefore, was to calculate the prevalence of MDR strains in new culture positive PTB cases.

Patient recruitment

This was an observational study involving new cases of PTB. New cases were defined as those with no history of Anti-Tuberculosis Therapy (ATT) intake in the past or intake for <1 month. All consecutive suspected PTB patients during the period of 2013-2016 from the Internal Medicine Outpatient Department, All India Institute of Medical Sciences, New Delhi and National Institute of Tuberculosis and Respiratory Diseases, New Delhi were enrolled in the study after taking prior written consent. The ethics committee of both institutes gave approval before the study was started (Ethical Clearance number IEC/NP-62/2010).

TB diagnosis and microbiological tests

Complete blood count, Liver and Kidney function tests along with Chest X-Ray was done for all patients. The sputum specimens collected were decontaminated using standard decontamination protocol (N-acetyl-L-Cysteine-sodium hydroxide method). The pellet obtained after decontamination was used for Ziehl-Neelsen (ZN) staining smear microscopy [2]. Decontaminated sputum specimens were then used for culture inoculation on Lowenstein-Jensen (LJ) media and BACTEC MGIT™ 960™ (BD, Sparks, MD, USA) liquid culture media [3].

Materials and Methods

Keywords: MDR-TB; Pulmonary tuberculosis; Drug susceptibility

Conclusion:

There is a high burden of MDR strains among new PTB cases. A higher prevalence could be because centers were referral institutes.

References:

Mycobacterium tuberculosis was identified by slow growth rate, colony morphology, inability to grow on L-J media containing p-nitrobenzoic acid (500 µg/ml), niacin and catalase tests immuno-chromatographic test kit (SD MPT64TB Ag kit, Standard Diagnostics, Gyeonggi-do, South Korea) for liquid culture. All culture-positive specimens (liquid or solid) were further subjected to DST for first-line anti-TB drugs using genotypic [Line Probe Assay (LPA)] and phenotypic methods.

Drug susceptibility testing (DST) was carried out on L-J media by an economic variant of 1% proportion method [4]. Drug susceptibility was tested at a concentration of 40 µg/ml Any strain with 1% (critical proportion) of bacilli resistant to the drugs was classified as resistant to the drug.

Statistical analysis
Data were analyzed using STATA v12.2 (StataCorp, College Station, Texas, USA). Mean and SD was calculated for data following normal distribution while median and range were calculated for data not normally distributed.

Results
Out of 1103 patients recruited, there were 649 (59%) males and 454 (41%) females. The median age was 34 (10-80) years. Baseline data is given in Table 1. A total of 508 (46.1%) and 595 (53.9%) were smear-negative and positive respectively, of which 166/508 (32.7%) and 547/595 (95.9%) were culture positive, respectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TB patients (n=1103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (Range) in years</td>
<td>34 (10-80)</td>
</tr>
<tr>
<td>Male</td>
<td>649 (59%)</td>
</tr>
<tr>
<td>Female</td>
<td>454 (41%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>117 (11%)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>314 (28%)</td>
</tr>
<tr>
<td>Non-smoker-</td>
<td>584 (53%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>93 (8%)</td>
</tr>
<tr>
<td>Blood investigations</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (gm/dl)</td>
<td>12.3 ± 1.2</td>
</tr>
<tr>
<td>Platelet count (cells/ul)</td>
<td>167.7 ± 36.3</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm in 1st hour)</td>
<td>14.9 ± 2.5</td>
</tr>
<tr>
<td>Total lymphocyte count (cells/ul)</td>
<td>6.3 ± 1.8</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>22.8 ± 10.4</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>139.7 ± 6.6</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dl)</td>
<td>0.39 ± 0.18</td>
</tr>
<tr>
<td>Total protein (gml/dl)</td>
<td>7.7 ± 1.6</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>4.7 ± 0.4</td>
</tr>
</tbody>
</table>

Any resistance to Rifampicin 62/683 9.10%
Any resistance to Isoniazid 75/683 11%
MDR-TB 60/683 8.70%

Table 1: Baseline demographic data.

Table 2: Resistance prevalence.

Discussion
India contributes nearly one third to the total TB case burden and has the highest number of new reported TB and MDR-TB cases in the world [1]. There have been various studies reporting the prevalence of MDR-TB in India with a range of 0.6% to 24% MDR-TB in new TB cases [5-7]. The proportion of MDR TB patients with the history of intake of ATT in the past varied from 8% to 67% [8-11]. Though these studies have been conducted in different parts of India, they indicate an increasing prevalence of MDR TB cases, in agreement with global data [1]. A recent meta-analysis showed that prevalence of MDR-TB has increased from 4.1% of total new cases in 1995-2005 to 5.6% cases in 2006-2015. Majority of these studies had used culture as the technique for DST [12]. Incomplete and unsupervised treatment, poor follow up and misconceptions about TB treatment, poor nutrition and social support, lack of political commitment are some of the reasons responsible for increasing resistance [1]. With the current practices of TB treatment in India, it is estimated that incidence of MDR-TB could increase from 3.9 cases/100 000 population [95% Confidence Interval (CI)] currently to as high as 14.1 cases/100 000 population (95% CI 11.2-16). In the same study, it was hypothesized that the rate of primary transmission of MDR strain would increase from 15% to 85% of total MDR cases [13].

The wide range of resistance prevalence from different parts of India indicates the lack of uniform surveillance methodologies across the country. Realizing this necessity, the first national drug resistance survey was conducted by the Revised National Tuberculosis Programme (RNTCP) from 2014-2016 [14]. It recorded the prevalence of any Isoniazid resistance and MDR strains in new PTB cases (n=3065) to be 11.6% and 2.84% respectively. In our study, the prevalence of Isoniazid resistance was the same but MDR was almost three-times. This could be due to our laboratory being a referral center and subsequent referral bias.
Such studies are important to be done in high TB burden countries like India which have limited resources and are experiencing the increased burden of both communicable and non-communicable diseases. MDR-TB treatment reaches <30% of the target population in India currently [1], with successful treatment in only 46% of cases in 2015. One in every five (20%) patients on MDR-TB treatment died or was lost to follow up [15]. This has been a major issue needing addressal which led to RNTCP launching the Programmatic management of Drug-Resistant TB (PMDT) guidelines in 2017 [13].

Our findings emphasize the importance of continuing the systematic surveillance of TB to monitor the trends of drug resistance in India, with appropriate direction of resources to drug-resistant TB.

Conclusion

There is a high prevalence of MDR-TB in new pulmonary TB patients. Since both centers were tertiary care and referral institutes, this result might not be reflective of the general patient population.

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