Prevalence of primary drug resistant *Mycobacterium tuberculosis* in Mashhad, Iran

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**Background & objectives:** Multidrug resistant tuberculosis (MDR-TB) has been a cause of concern in both developed and developing countries. Surveillance data on primary drug resistance in *Mycobacterium tuberculosis* are important to design tuberculosis control programmes. There is a paucity of information about primary drug resistance in mycobacterium in Iran. We undertook this hospital-based study to assess the prevalence of primary of drug resistant in *M. tuberculosis* in Mashhad, Iran.

**Methods:** A total of 105 *M. tuberculosis* isolates from cases with pulmonary and extrapulmonary tuberculosis, who did not have prior history of anti-tuberculosis treatment, were tested for the drug susceptibility by indirect proportion susceptibility test as per the standard guidelines.

**Results:** Of the 105 isolate tested, 93 were from pulmonary specimens; and the remaining were extrapulmonary. 79.6 per cent of pulmonary and 50 per cent of extrapulmonary specimens were smear positive. Resistance to at least one drug was shown by 29.5 per cent, while 2.9 per cent were resistant to more than one drug. MDR-TB was found at 1 per cent of strains.

**Interpretation & conclusion:** Our study showed a high level of resistance to streptomycin and very low resistance to other drugs. To achieve the higher cure rate, replacement of streptomycin by ethambutol and strict implementation of DOTs may be considered.

**Key words** Ethambutol - isoniazid - multidrug resistance - *Mycobacterium tuberculosis* - rifampicin - streptomycin

Worldwide emergence of multidrug resistant *Mycobacterium tuberculosis* (MDR-TB) has been reported in both developed and developing countries. These isolates resistant to both rifampicin (RMP) and isoniazid (INH) with or without resistance to other drugs, have caused concern worldwide due to high mortality, particularly in persons co-infected with the human immunodeficiency virus (HIV). Continuous surveillance of the primary and acquired drug resistance patterns of *M. tuberculosis* is important in assessing the efficacy of chemotherapy regimens used in past years as well as in detecting problems in past treatments. The absence of a surveillance network and inadequacy of reliable prevalence
studies in Iran make it difficult to evaluate the true extent of MDR-TB in the country. The present study was undertaken to measure the prevalence of primary drug resistant *M. tuberculosis* at a large hospital in Mashhad, the second largest city of Iran.

**Material & Methods**

A total of 105 *M. tuberculosis* isolates obtained from tuberculosis patients referred during 2001-2002 to Ghaem multispeciality hospital affiliated to Mashhad University of Medical Sciences and Health Services, Mashhad, North East Iran receiving referral patients from five millions population of South, North and Razavi Khorasan provinces were included in this study.

A total of 2682 specimens, 2376 (88.6%) pulmonary specimens (sputum, broncho-alveolar lavage and gastric lavage) and 306 (11.4%) extrapulmonary specimens (pleural effusion, pericardial effusion, joint aspirates, urine, lymph node biopsy), were collected from patients undergoing investigations for possible active tuberculosis. The WHO/IUATLD guidelines were used for direct microscopy, culture, strain speciation and drug sensitivity test.\(^7,8\)

Of the total 2682 specimens tested, 192 were culture positive. Of these 192, 105 *M. tuberculosis* isolates were selected for susceptibility testing to first line anti-tuberculosis drugs; isoniazid (INH), rifampicin (RMP), ethambutol (EMB) and streptomycin (STM); based on having no previous history of treatment with anti-tuberculosis drugs and possibility of further follow up. The method of proportions, using the indirect technique, was used to evaluate drug resistance\(^7\). The drug concentrations were 0.2, 40.0, 2.0 and 4.0 µg/ml for INH, RMP, EMB and STM, respectively. Internal controls were used to ensure the quality of drug susceptibility test.

Standard questionnaire was used to determine the history of previous anti-TB drug therapy and the patients were categorized as having either initial or acquired resistance, according to the standard definitions\(^8\). Resistance to a particular drug with or without resistance to other anti-TB drugs was denoted as any resistance. Resistance to isoniazid and rifampicin with or without resistance to other anti-TB drugs was defined as multi-drug resistance.

The ethical committee of the university approved the study protocol.

**Results**

The drug susceptibility test and demographic data of 105 isolates and corresponding patients were analyzed. The results showed that 93 (88.57%) isolates were obtained from pulmonary and 12 (22.43%) from extrapulmonary specimens; 55 (51.43%) isolates were from males. The mean age of patients was 56.62 ± 17.66 yr; 79.6 per cent of pulmonary and 50 per cent of extrapulmonary specimens were smear-positive. Sixty five (42.9%) patients were hospitalized and others were outpatients, of which two were prisoners.

<table>
<thead>
<tr>
<th>Specimen (n)</th>
<th>Smear</th>
<th>Sensitive to 4 drug</th>
<th>Resistant to SM alone</th>
<th>Resistant to INH alone</th>
<th>Resistant to EMB &amp; MS</th>
<th>Resistant to INH.EMB &amp; SM</th>
<th>Resistant to all drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (93)</td>
<td>+</td>
<td>51 (68.9)</td>
<td>19 (25.7)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>12 (63.2)</td>
<td>7 (36.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extra- pulmonary (12)</td>
<td>+</td>
<td>6 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (105)</td>
<td></td>
<td>74 (70.5)</td>
<td>27 (25.7)</td>
<td>1 (0.95)</td>
<td>1 (0.95)</td>
<td>1 (0.95)</td>
<td>1 (0.95)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages
SM, streptomycin; INH, isoniazid; EMB, ethambutol
Of the 105 isolates tested, 31 (29.5%) showed resistances to at least one drug or more than one drug of which, one (0.95%) was MDR. In a group of 80 isolates from patients with pulmonary tuberculosis, 57 (71.3%) were sensitive to all drugs while 19 (23.75%) showed resistance to STM alone; one (1.3%) to INH; one (1.3%) to ETM and STM; one (1.3%) to INH, ETB and STM; and one (1.3%) was resistant to all drugs. None of the isolates were resistant to ethambutol or rifampicin alone. Among the 12 isolates from patients with extrapulmonary tuberculosis, 11 were sensitive to all drugs and 1 were resistant to STM alone.

Discussion

The prevalence of primary drug resistance among MTB isolates was low in Mashhad. This is fairly similar to the median of anti-tuberculosis drug resistance mentioned in the second WHO report\(^9\). This may be due to strict implementation of DOTS for the past decade in our region and also good compliance of patients to treatment. Another reason could be non availability of anti-TB drugs for prescription by the private physician. This helps in proper follow up of patients by health offices preventing treatment failures, and improper prescription of anti TB drugs for other infections leading to drug resistance. However, our results are at variance with those reported from our own region during the same period showing 3.02 per cent treatment failure\(^10\). This may be due to other reasons such as incorrect treatment, poor compliance and erratic drug ingestion, poor drug absorption or shortages of anti-TB drugs\(^11\) which were not considered in that report.

Our finding of about 1 per cent MDR-TB is different from the 5 per cent reported for Iran in the second WHO Global report\(^9\). The possible explanations for this disagreement is that WHO study involved foreign population also and they contributed about half of the MDR-TB isolates\(^9\), while in our study, majority of patients were Iranian and only 5 were Afghan refugees. The study also showed a high prevalence of resistance to STM among MTB isolates. This is not surprising because this drug has been used for many years for treatment of many infectious diseases including brucellosis and tuberculosis. HIV screening was done only for two intravenous (IV) drug abusers and one was found positive for HIV and both harboured isolates susceptible to all 4 anti-TB drugs.

In conclusion, our study showed a high primary resistance to STM and very low resistance to other drugs. As the prevalence of resistance to STM was high, we suggest replacement of this drug with ETB to obtain better results.

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