DRUG RESISTANCE PATTERNS OF MYCOBACTERIUM TUBERCULOSIS COMPLEX STRAINS ISOLATED DURING AN ELEVEN YEAR PERIOD IN A FACULTY HOSPITAL IN ISTANBUL

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ABSTRACT
One thousand eight hundred and forty three Mycobacterium tuberculosis complex (M.tuberculosis) strains isolated between 1992-2002 from 27,436 clinical specimens were evaluated for their drug resistance to streptomycin (S), isoniazid (H), rifampin (R) and ethambutol (E). The drug resistance of 1843 M.tuberculosis strains was assessed by radiometric proportion method in Bactec 460 TB system(Becton Dickinson). Resistance to one or more of the drugs was found in 594(32.23 %) strains. Resistance to H among the other drugs was the most common (27.07 %). The number of multidrug resistant M.tuberculosis strains was detected as 283 (15.35 %) within total strains. The results obtained in this study show that the rate of resistant strains circulating in the community are very high, so, we concluded that the national tb control programme must be reexamined urgently in our country.

Introduction
Tuberculosis (tb) remains one of the deadliest disease in the world. Drug-resistant tb is a significant threat to tb control because only a few effective drugs are available against M.tuberculosis. The prevalence of multidrug resistant-tb (MDR-tb) increases tenfold after unsuccessful treatment of new tb cases (1). Thus, the highest priority in fighting MDR-tb is its prevention by appropriate treatment (2). In regions with a high prevalence, the realisation of a drug resistance test is very important for correct management and for monitoring levels of resistance (3). The global magnitude of drug-resistant tb has not been well studied until recently. In 1994 WHO and IUATLD launched the global project on antituberculosis drug resistance surveillance to determine the levels of resistance to H, R, E and S in nationally representative populations (4,5). Findings indicated that MDR-tb continues to be a serious problem especially in Estonia, Latvia, Russia, China and Iran (6,7). Turkey was not among the countries surveyed. Reports from our country have shown high levels of drug resistance (8-10). Tb is an important health problem in Turkey. The incidence of tb was 27/100.00 in Turkey in 2000 (11) and the last prevalence study was published in 1982 and it was found to be as 3.56 % (12). Istanbul is the biggest city in Turkey with a population of 16 million and Istanbul University, Istanbul Medical Faculty is one of the biggest University hospitals in our city. The tb laboratory in the Department of Microbiology and Clinical Microbiology accepts an average of 2500 specimens from patients suspicious for tb per year. The purpose of this retrospective study was to review anti-tb drug resistance patterns to four
first line drugs of *M.tuberculosis* complex strains isolated in our laboratory during an 11 year period.

**Materials and Methods**

A total of 27,436 clinical specimens were processed between 1992-2002 at the department. Nonsterile clinical specimens were decontaminated and digested with N-acetyl-L-cysteine/NaOH. All specimens were inoculated onto Löwenstein-Jensen and liquid radiometric media (Bactec 460 TB, Becton Dickinson, Sparks, MD, USA). Cultures were incubated at 37 °C and discarded after 8 weeks if no growth occurred. Strains were identified as *M.tuberculosis* complex and non-tuberculous mycobacteria by the Bactec NAP identification test. Susceptibility testing of the *M.tuberculosis* complex and non-tuberculous mycobacteria by the Bactec NAP identification test. Susceptibility testing of the *M.tuberculosis* complex strains was performed on each isolate for H (0.1 µgr/ml), R (2 µgr/ml), S (2 µgr/ml) and E (2.5 µgr/ml) in Middlebrook 7H12 medium by the radiometric proportion method and a control vial containing 1:100 dilution of the inoculum with no drugs was set up for each strain.

**Results and Discussion**

During the 11 year period a total of 1843 *M.tuberculosis* complex strains were isolated from 27,436 specimens (6.7 %). Resistance to one or more of the drugs was found in 594 (32.23 %) isolates. Resistance to H was the most common; in 499 strains (27.07 %), followed by R; in 313 strains in (16.98 %) and E; in 256 strains (13.89 %). Resistance to S was found to be the lowest; in 229 strains (12.42 %). Drug resistance patterns of *M.tuberculosis* complex strains are presented in the Table.

By 2000, WHO estimated that the number of new cases of tuberculosis had risen to 8.7 million (13).Susceptibility pattern of *M.tuberculosis* isolates against antimycobacterial drugs are of important value for clinical and control decisions. MDR is associated with a lower percentage of cures and a high death rate (14). In this retrospective study the total resistance rate to one or more of the drugs found to be as 32.33 % and this result was similar with that of some other studies in Turkey (30.4%- 39.2 %) (8,10,15), although lower rates (14.9 %-25 % ) have also been reported (16-18). Reasons of these differences in our country could be due to variations in patients characteristics like geographical origin and compliance , susceptibility testing methods performed or treatment failures. The high resistance rate of this study were close to the rates reported from Eastern European countries with poor tb control programs (Estonia 31.21 %, Latvia 41.6 %) included in the global surveillance report (1).The rate of total MDR strains (15.35 %) was also similar to the results of Estonia (11.7 %) and Latvia (22.1 %) (1). The rates of MDR strains in some of the published studies from Turkey were declerated between 2.7-19.7 % (9,10,18,19). The highest rates of MDR

<table>
<thead>
<tr>
<th>Resistance patterns</th>
<th>Total strains (%)</th>
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<tbody>
<tr>
<td>Fully susceptible</td>
<td>1249 (67.78)</td>
</tr>
<tr>
<td>Single drug resistance</td>
<td>230 (12.47)</td>
</tr>
<tr>
<td>S</td>
<td>50 ( 2.71)</td>
</tr>
<tr>
<td>H</td>
<td>139 ( 7.5)</td>
</tr>
<tr>
<td>R</td>
<td>27 ( 1.46)</td>
</tr>
<tr>
<td>E</td>
<td>14 ( 0.75)</td>
</tr>
<tr>
<td>Two drug resistance</td>
<td>124 ( 6.72)</td>
</tr>
<tr>
<td>SH</td>
<td>40 ( 2.17)</td>
</tr>
<tr>
<td>HR</td>
<td>59 ( 3.2)</td>
</tr>
<tr>
<td>HE</td>
<td>21 ( 1.13)</td>
</tr>
<tr>
<td>RE</td>
<td>3 ( 0.16)</td>
</tr>
<tr>
<td>SE</td>
<td>2 ( 0.10)</td>
</tr>
<tr>
<td>Three drug resistance</td>
<td>143 ( 7.75)</td>
</tr>
<tr>
<td>SHR</td>
<td>24 ( 1.3)</td>
</tr>
<tr>
<td>HRE</td>
<td>103 ( 5.58)</td>
</tr>
<tr>
<td>SHE</td>
<td>16 ( 0.86)</td>
</tr>
<tr>
<td>Four drug resistance (SHRE)</td>
<td>97 ( 5.26)</td>
</tr>
<tr>
<td>MDR</td>
<td>283 (15.35)</td>
</tr>
</tbody>
</table>
strains in international papers were reported from Nepal (48 %), India (34 %), New York City (30 %) and Korea (15 %) (6). The MDR strains isolated in this study were mostly resistant to three or more of the drugs so, this must be kept in mind while planning the treatment regimen of patients with suspected MDR-tb in our region. The total rate of the resistance to four drugs in our study (5.26 %) was also significantly more higher than reported in the median rate of the global surveillance report (0.8 %) (1). H was the drug with the highest resistance rate (27.07 %). This finding is paralleled to other studies (20-25). However some studies have reported R (26,27), S (28-30) or E (31) as having the highest resistance. In our study S was the drug with the lowest total resistance rate (12.42 %). Although there are not so much difference between the total resistance of S and E (13.89 %), S may be prefered over E as the forth drug in the therapy regimen in our region. Single R resistance was detected in 27 (1.46 %) strains. R resistance together with E was detected in only 3 (0.16 %) strains. Because single R resistance and R resistance together with first line drugs other than H was found only in a limited number of strains, detecting of R resistance could be accepted as a good marker for MDR-tb in our region. A history of tb treatment is the strongest predictor of MDR-tb. In one study, while previously treated patients had a 30 % rate of MDR-tb, patients who had not received prior treatment had a 7 % rate (32). Although we don’t have any data about the treatment regimens and adherence of our patients, it is known that poor compliance to tb-therapy is a major problem in our region (33). Direct observed treatment (DOT) is not applied in Turkey and fixed dose combination tablets are not to be found. Surveillance of drug resistance in M.tuberculosis is very important for the evaluation of the quality of tb control. We consider to report the combined prevalence of drug resistance, which may well reflect the overall number of circulating strains in the community and we concluded that, the high resistance rates found in our study are an indicator of poor national tb control programme in our country.

REFERENCES

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